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The American Journal of Medicine

Vol. XII MAY, 1952 No. 5

Symposium on Multiple Sclerosis and Demyelinating Diseases

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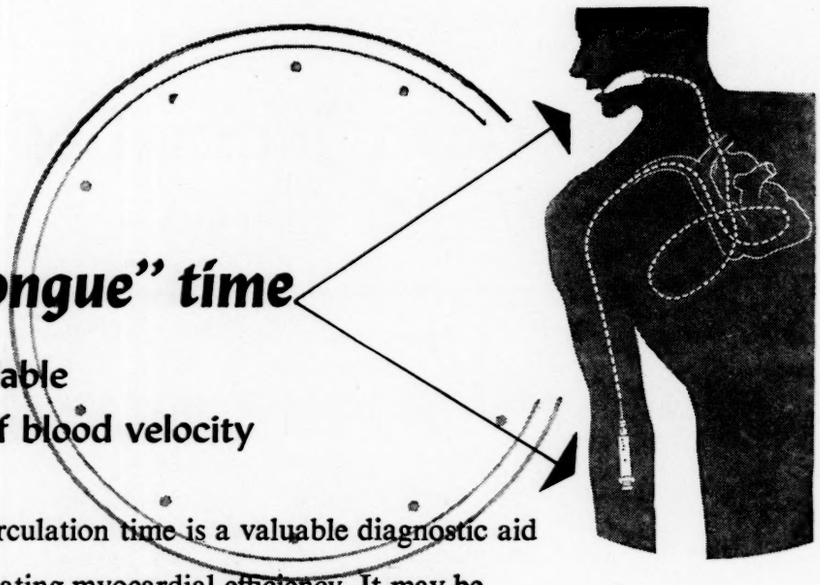

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The American Journal of Medicine

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The demyelinating diseases have been, by and large, the forgotten problem of the medical world. The publication of this symposium is evidence of the awakened interest in this field.

The National Multiple Sclerosis Society was formed in 1946 for the purpose of stimulating interest in the problems of the demyelinating diseases and to encourage and support fundamental and clinical research in these diseases. We are gratified to report that the aims of the Society are being gradually fulfilled. That there has been a renaissance of productive activity in this field is evidenced by the many recent publications in this field: the present Symposium on Multiple Sclerosis, the Proceedings of the Association for Research in Nervous and Mental Diseases (1948), Multiple Sclerosis and the Demyelinating Diseases, the publication of a series of three special articles in the Journal of the American Medical Association dealing with Multiple Sclerosis by Dr. George A. Schumacher, and the creation by law of the National Institute of Health for Neurological Diseases and Blindness. Many research projects are presently being conducted under the aegis of the National Multiple Sclerosis Society, the National Institute of Health for Neurological Diseases and Blindness and by privately endowed foundations.

We are proud of our record of achievement of our original goals and are grateful to the contributors and publishers of this volume for their help in our common aim, which is the dissemination of knowledge in the field of the demyelinating diseases.

CORNELIUS H. TRAEGER, M.D., *Medical Director,*
National Multiple Sclerosis Society

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Dr. Potts here gives a concise account of the symptoms, diagnosis, indications for surgery and type of surgery in the tetralogy of Fallot. He discusses at some length the rationale of his operation, aortic-pulmonary anastomosis, emphasizes the importance of proper anesthesia and temperature control and gives a restrained estimate of the operative results.

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JOHN THOMAS, G. B. BROTHERS, R. S. ANDERSON AND J. R. CUFF 613

The association of arachnodactyly with aneurysm of the aorta, due to cystic and mucinous degeneration of the media, is of great interest. There is a pronounced tendency for these aneurysms to dissect, causing death at a relatively early age.

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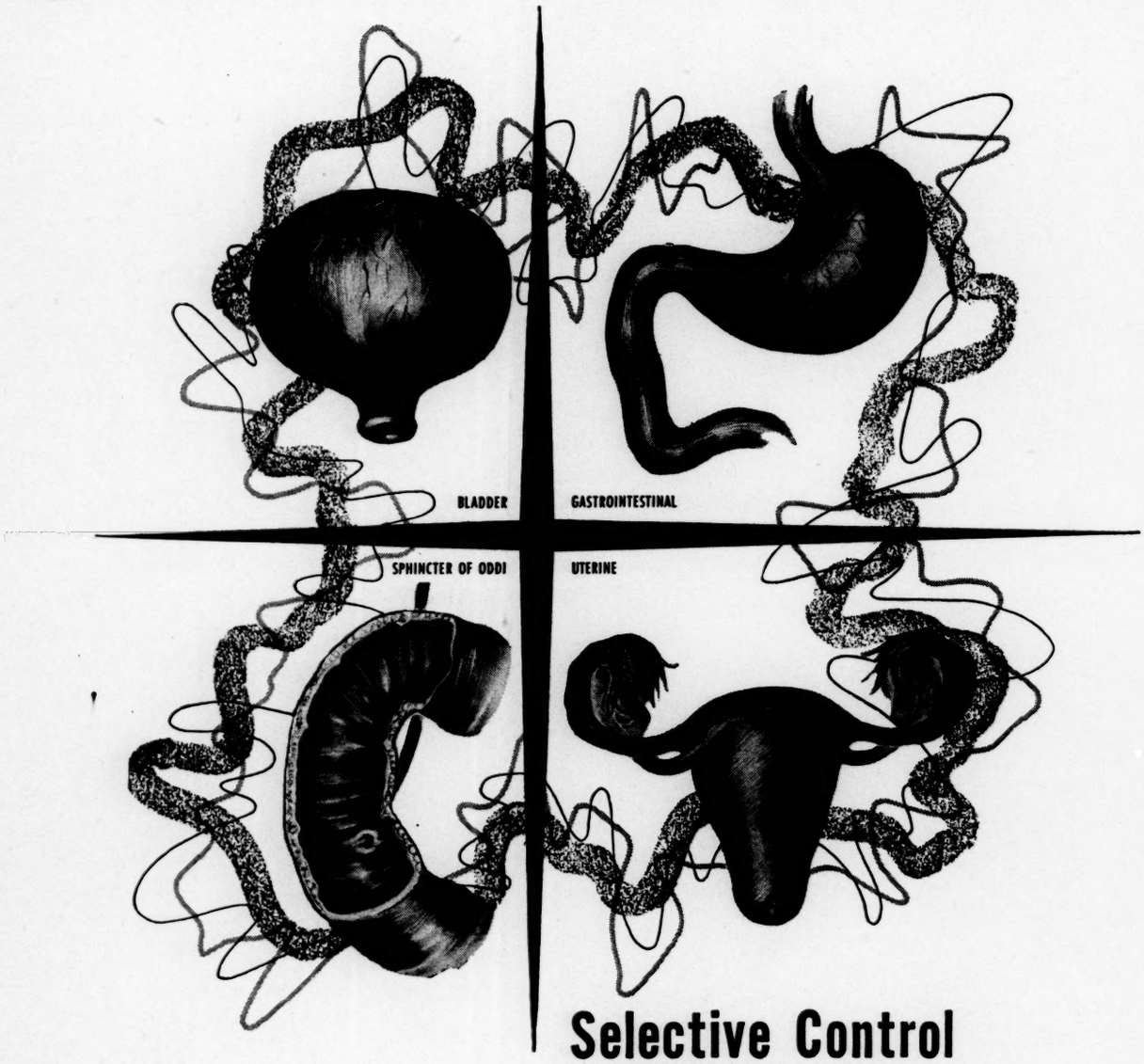

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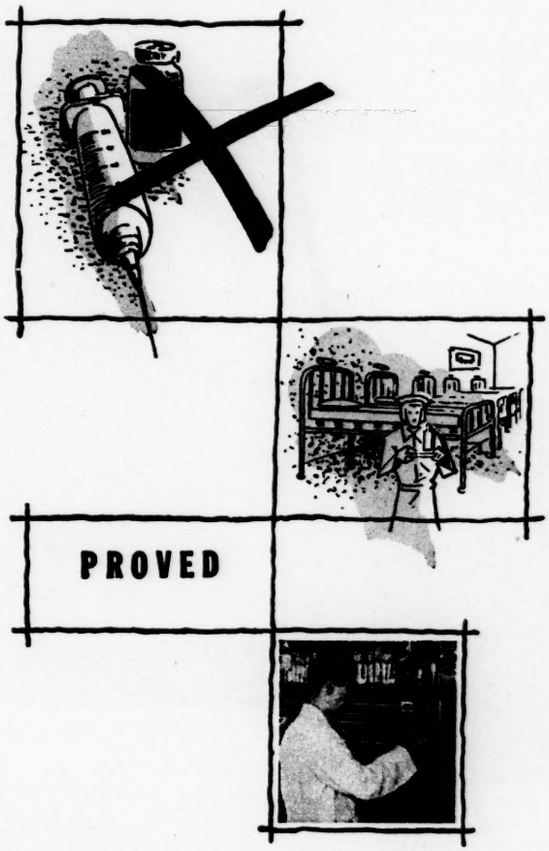

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*Cronheim, G., Justice, T. T., and King, J. S., Jr.. A New Approach to Increasing Tolerance of Oral Aminophylline—to be published.

*Justice, T. T., Jr., Allen, G., and Cronheim, G., Studies with Two New Theophylline Preparations—to be published.

**Waxler, S. H. and Schack, J. A., Administration of Aminophylline, J. A. M. A. 143:8, 736-739, June 1950 (This study does *not* refer to Aminodrox.)

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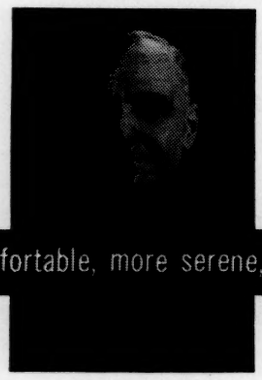

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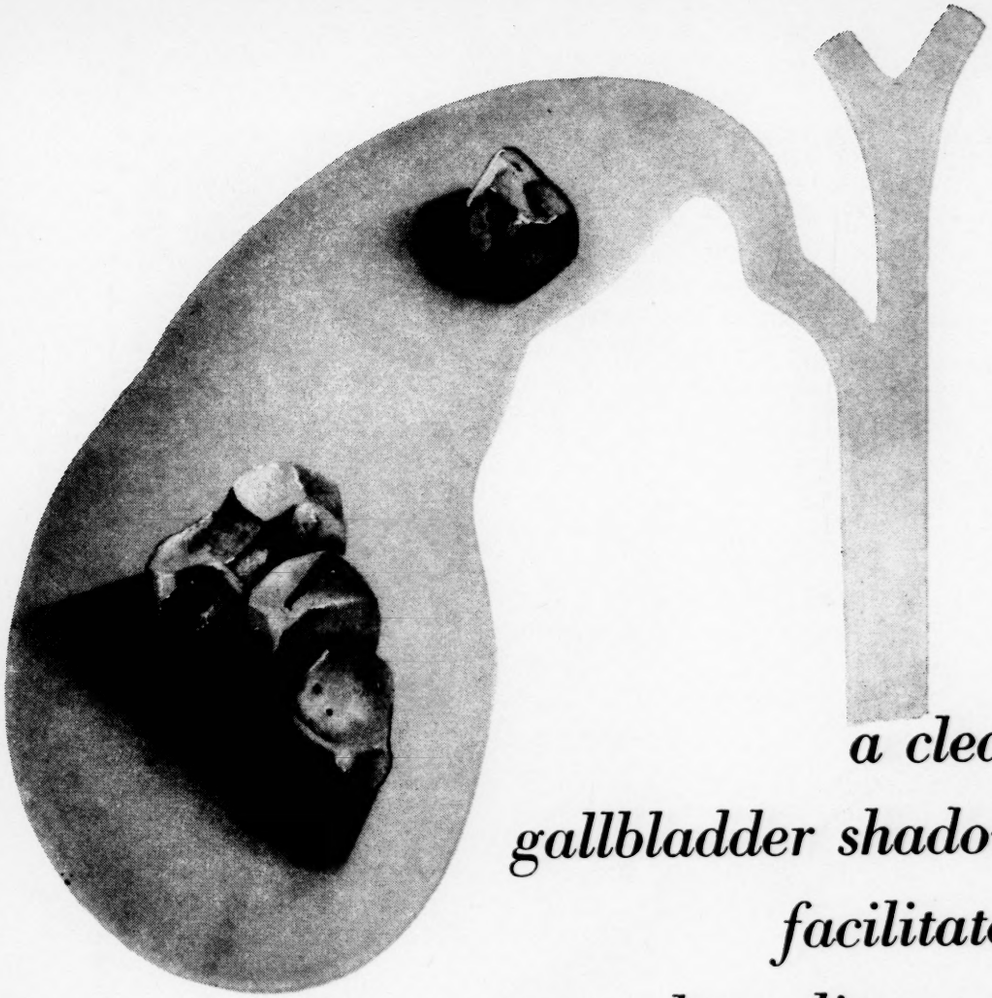

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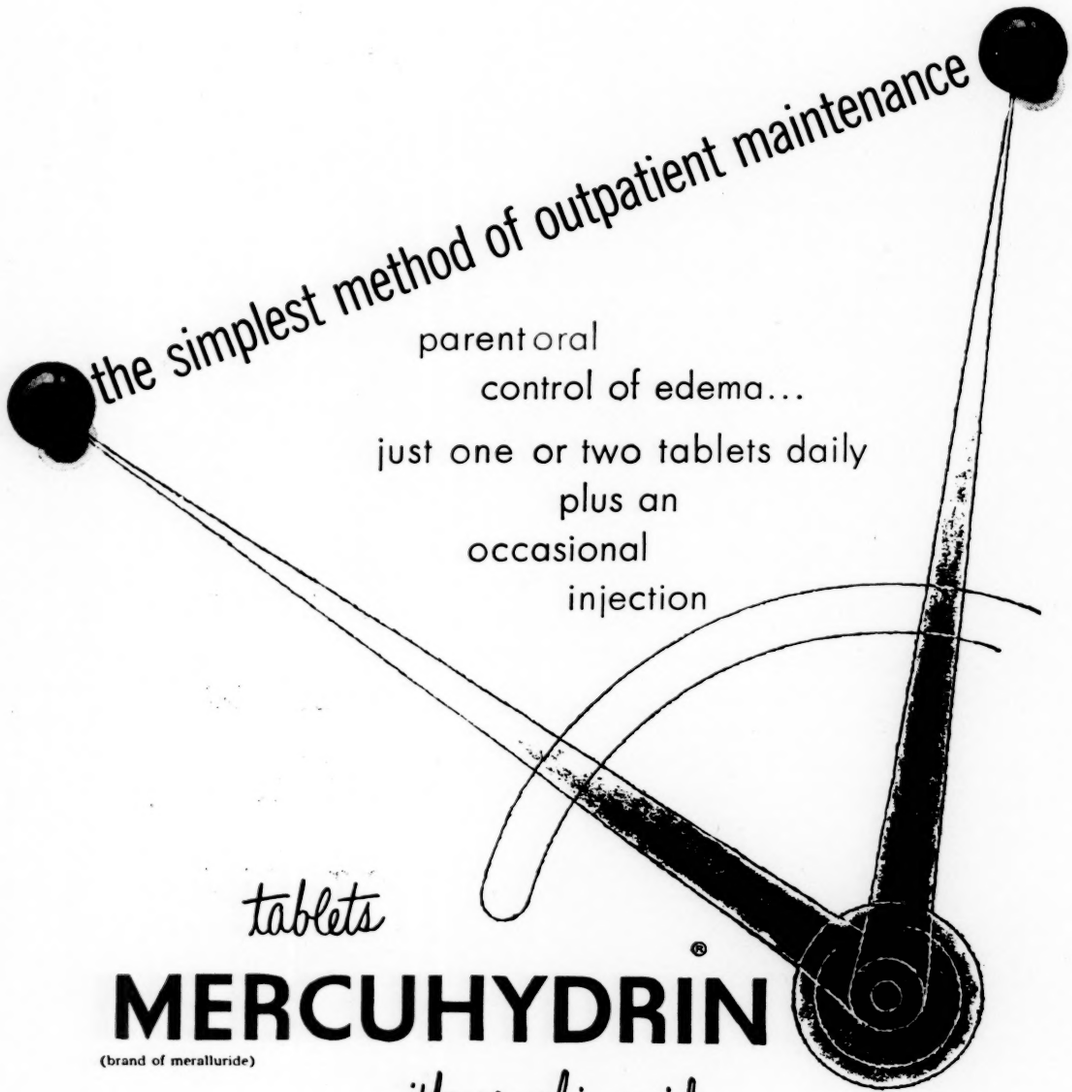

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1. J.A.M.A. 147:730-737 (Oct. 20) 1951. Literature and detailed dosage information on request.

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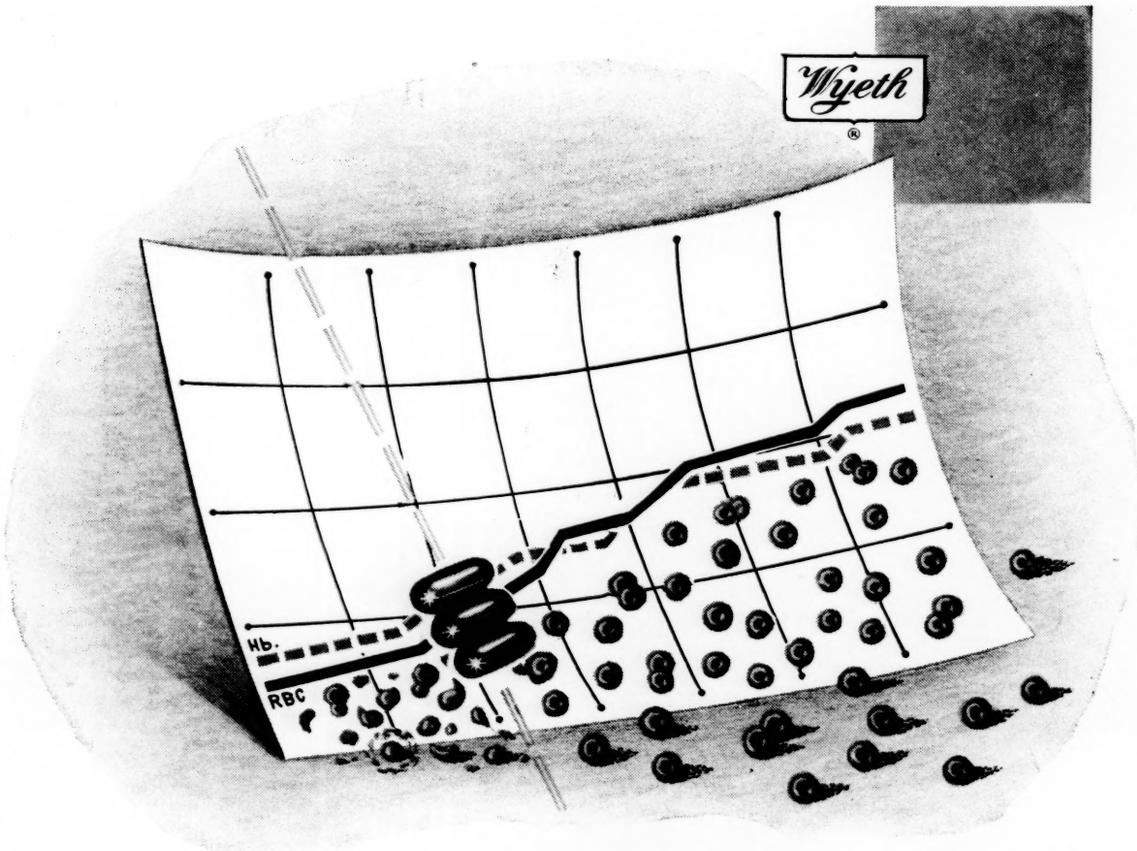

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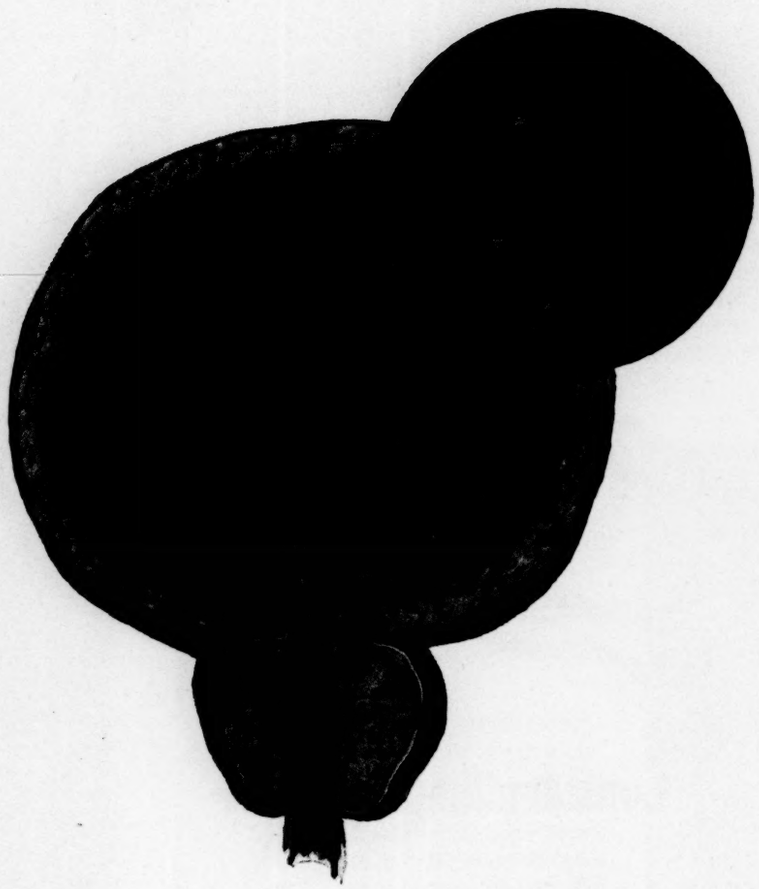
1. *Schaaf, R. S., Hurst, J. W., and Williams, C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1255 (Sept.) 1949*

Burroughs Wellcome & Co. (U.S.A.) Inc., *Tuckahoe 7, N. Y.*



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Blahey, P. R.: Canad. M.A.J. 66:151 (Feb.) 1952.

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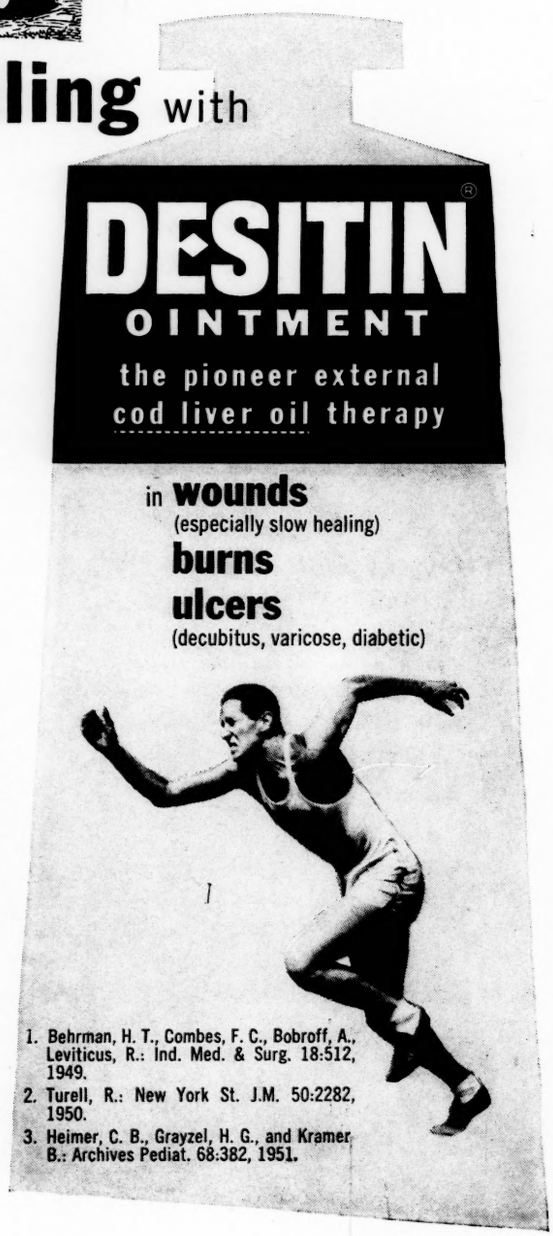

1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Turell, R.: New York St. J.M. 50:2282, 1950.
3. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives Pediat. 68:382, 1951.

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[1] New and Non-Official Remedies, 1951, American Medical Association.

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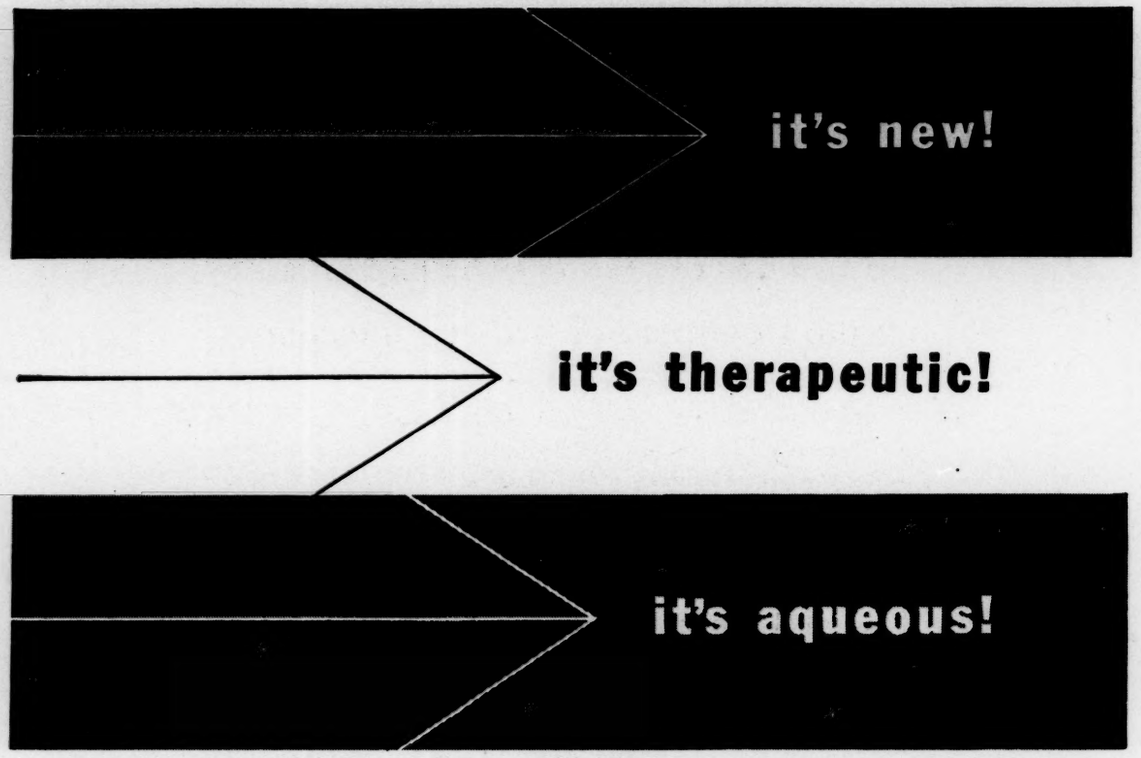

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Riboflavin (B_2)	5 mg.
Vitamin B_{12}	2 mcg.
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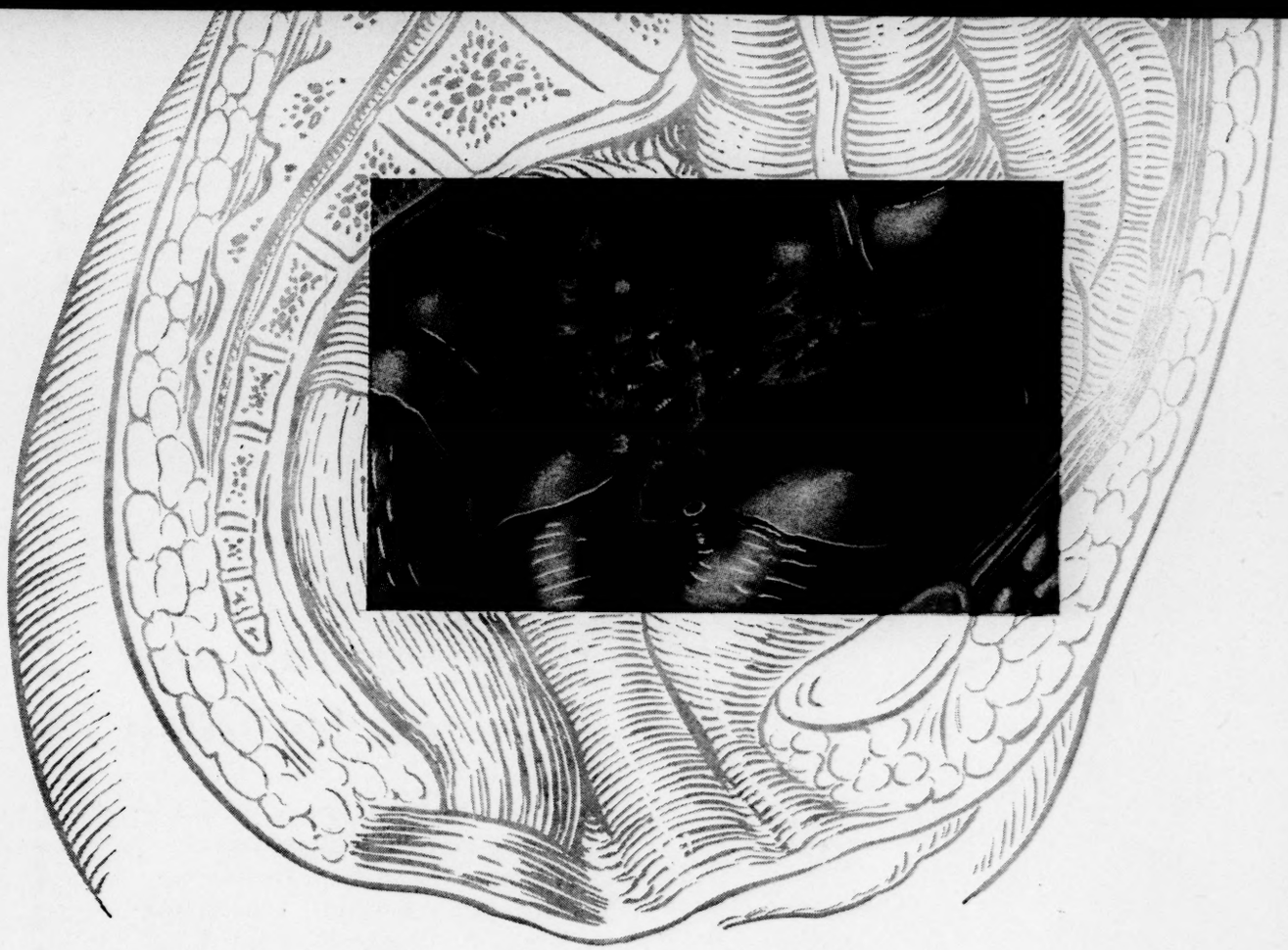

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1. Greene, C. C.: Kentucky M. J. *50*:8, 1952.
2. Stevenson, C. S., et al.: Am. J. Obst. & Gynec. *61*:498, 1951.

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Hamblen, E. C.: M. Clin. North America **32**:57 (Jan.) 1948.

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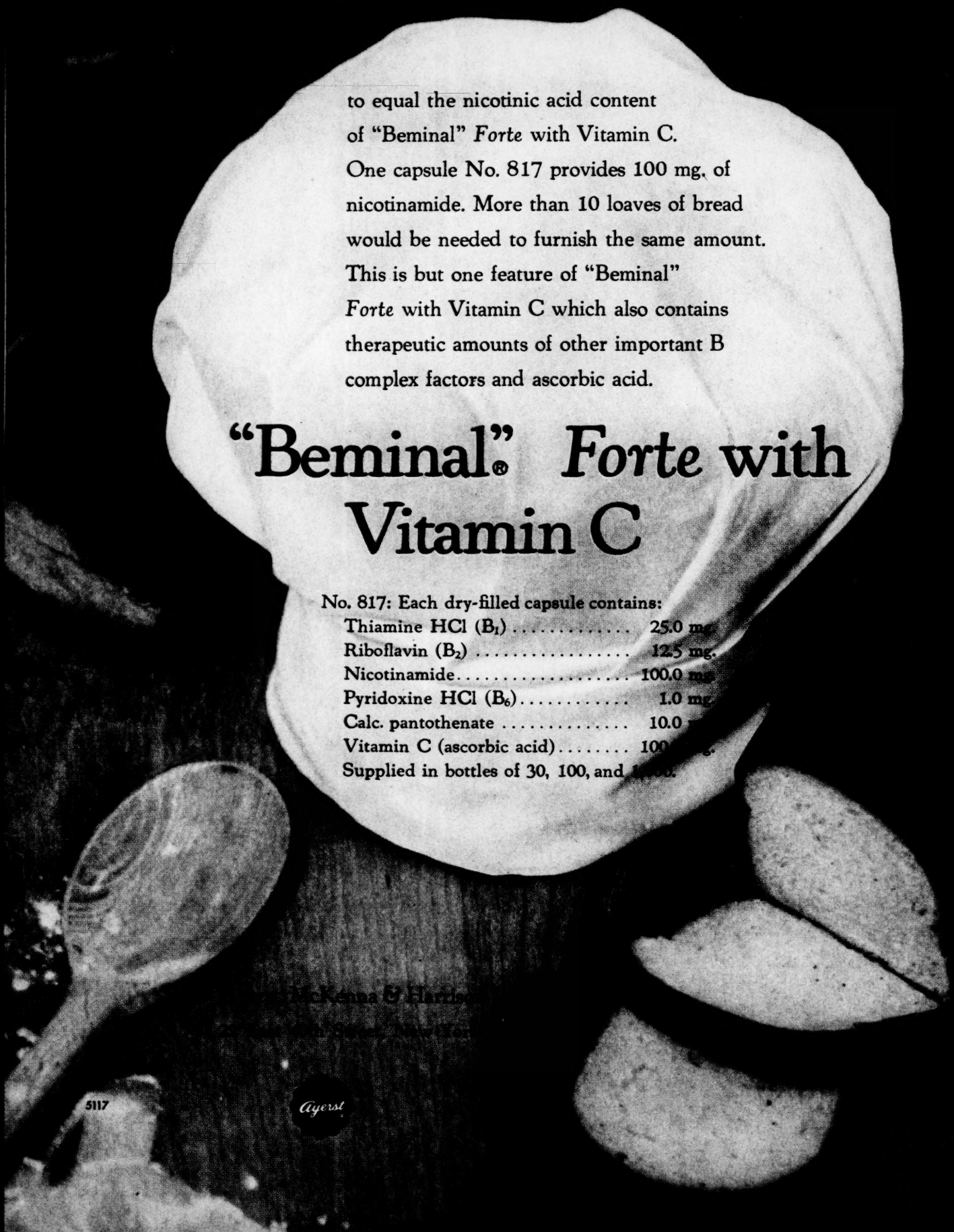

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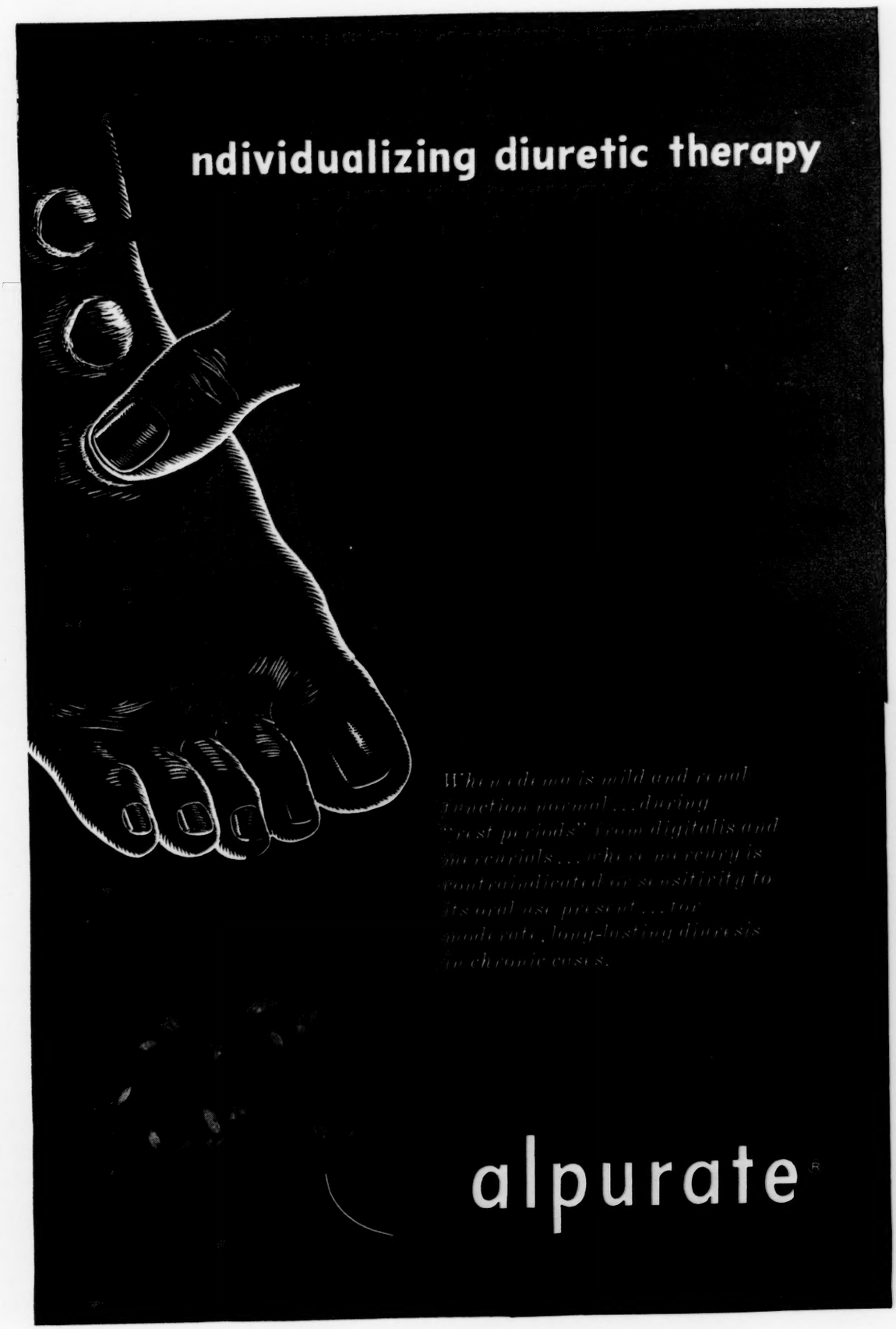
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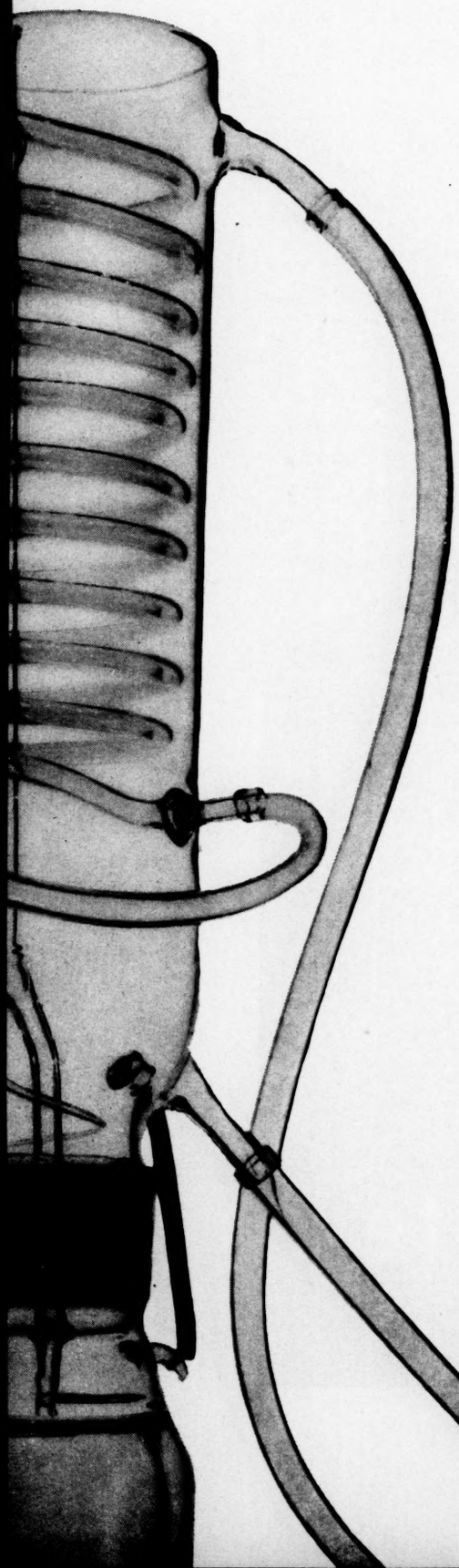

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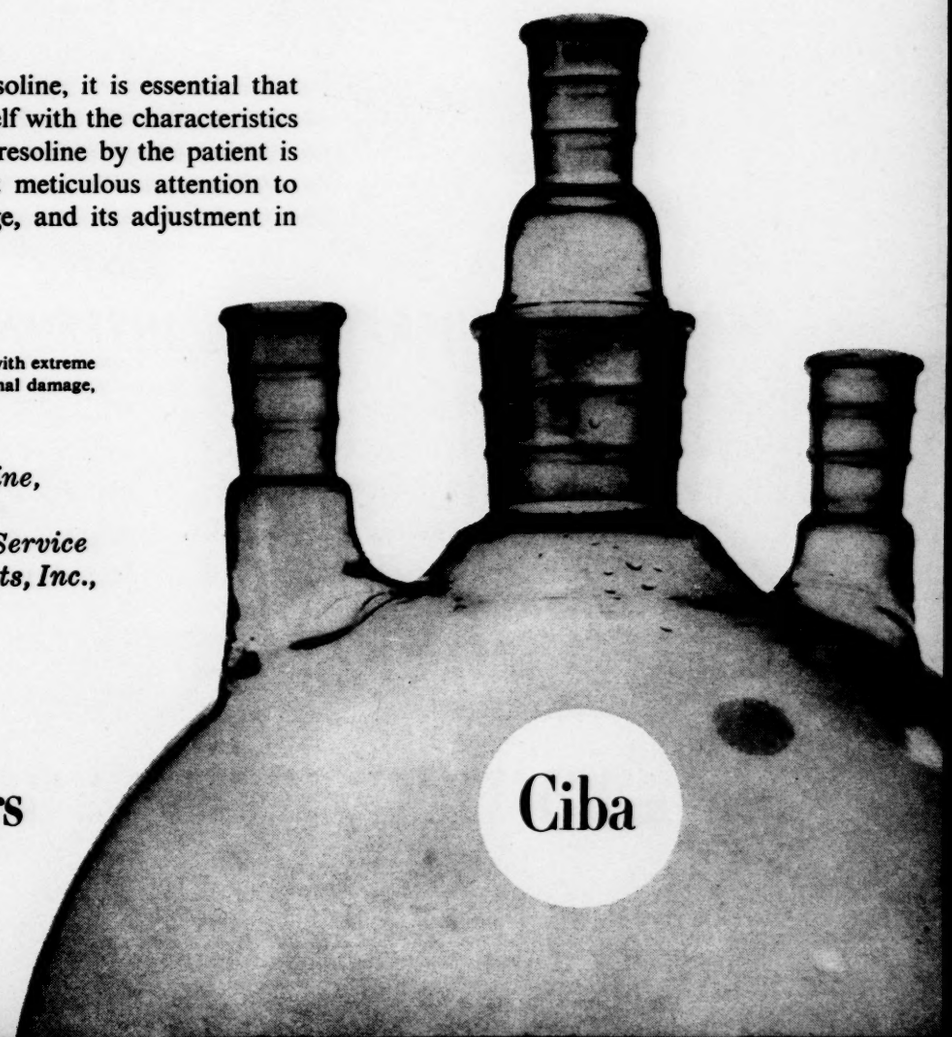

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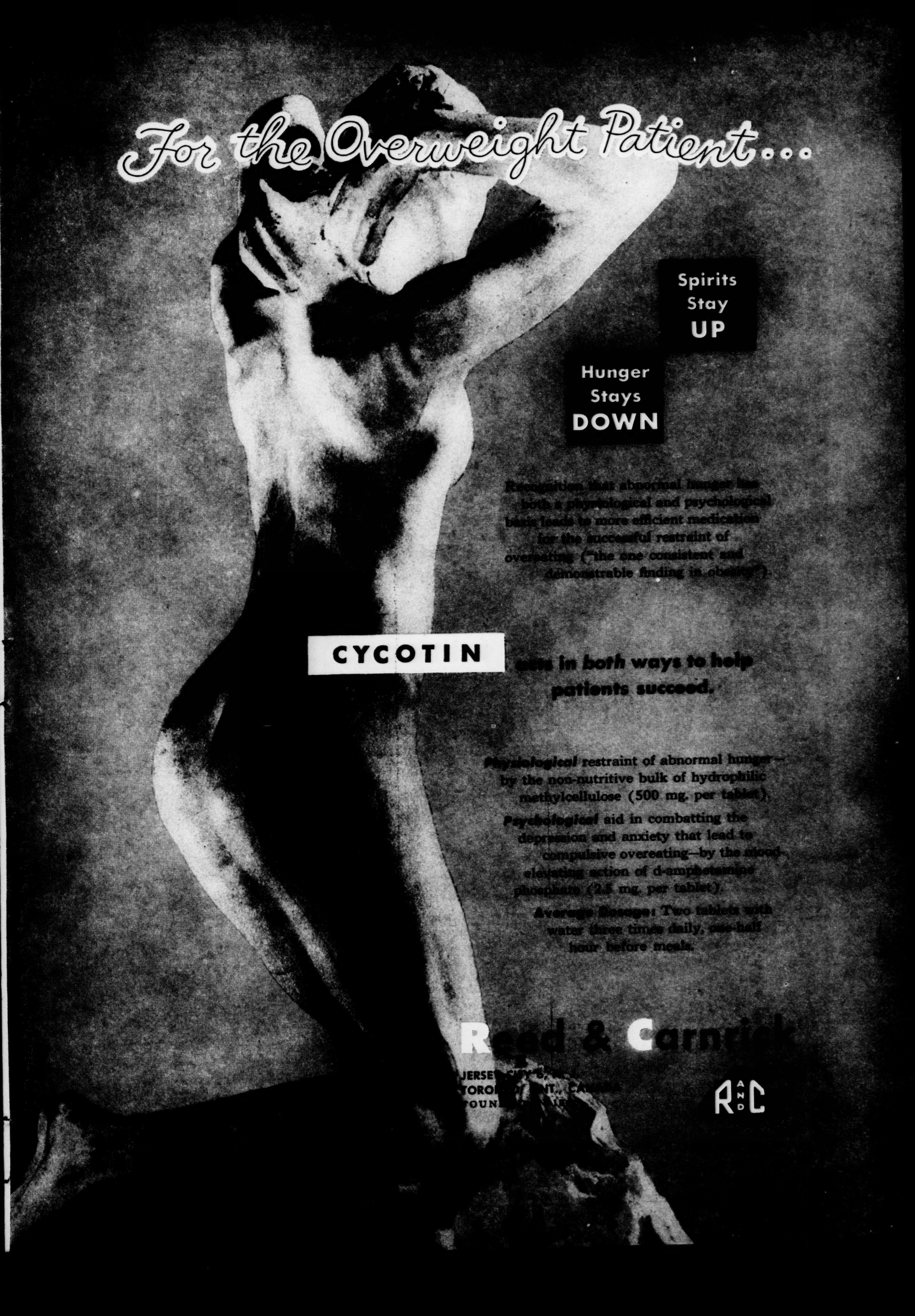
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The American Journal of Medicine

VOL. XII MAY, 1952 NO. 5

Foreword

GENERAL awareness among medical scientists and practitioners of the great prevalence of multiple sclerosis has been a surprisingly recent development in the history of the study of this disease. Although isolated investigators in the past quarter century devoted much energy and time toward an understanding of multiple sclerosis, it remained an esoteric problem of medicine generally neglected by the medical scientist and clinician alike. A common reaction of physicians to the disease was simply to reject the patient who had it. Treatment efforts were abortive in the sense that methods reported once were not often heard of again. Most recommended treatments fell by the wayside for lack of confirmation. Almost all had the failing of too few patients, observed too briefly and without satisfactory controls. The insistent demands by patients and their relatives, however, had the result that some methods did not fall by the wayside despite their probable uselessness.

Impetus for the first great wave of concentrated effort and research on a wide scale came from a group of laymen who in 1946 founded the National Multiple Sclerosis Society, an organization devoted to financing research in this field. When the available facts and hypotheses were assembled, it became evident that there was no meeting of minds on the questions of etiology, pathogenesis or treatment in multiple sclerosis. The only acceptable facts were those relating to the long familiar clinical course, the criteria for diagnosis and the descriptive facts of morbid anatomy. Most views about the pathogenesis of the disease were presumptive and inferential.

Over the past several years a fresh body of knowledge has been developing. Vital questions concerning fundamental aspects have been asked and intensive attacks on various facets of the problem launched. The aim of this Symposium is to delineate these problems, to pose pertinent questions and to bring into focus gaps in the fundamental knowledge concerning this disease and those conditions with which some believe it to be linked.

The problem of etiology in multiple sclerosis still encompasses virtually all of the great categories of causation of human disease, save for neoplasm and direct mechanical trauma—infection, inflammation due to allergic tissue responses, primary degeneration, degeneration secondary to primary vascular disturbances, deficiency states, hereditary predisposition to internal or external non-specific exciting causes, and psychogenic causes. Unique in the investigation of central nervous system disease not clearly due to a transmissible infectious agent has been the intensive epidemiologic study made of multiple sclerosis. The constant hope in these studies has been to uncover clues as to etiology. Striking epidemiologic characteristics have been established. These must be explained by any proposed theory of causation.

The rapid increase in knowledge concerning body reactions and indeed bodily disease resulting from life stress and associated emotional factors has led to the most careful scrutiny of the role of such factors both in the causation and treatment of multiple sclerosis. Data of such importance have been obtained as to make this aspect of investigation one of the most important single advances in the understanding and management of patients with multiple sclerosis; yet it seems unlikely that the disease will turn out to be primarily a psychosomatic disorder.

Great interest and a large body of investigation have been devoted to the basic problem of the meaning of demyelination, a conspicuous feature in multiple sclerosis. Serious questions are being raised about the importance of demyelination as an indicator of specific or limited etiology. Is it a specific common denominator relating the several central nervous system diseases in which it occurs, or is it a non-specific reaction of nervous tissue to injury consequent upon dis-

ruption of enzyme systems through various causes? To gain a clearer understanding of the problem and in attempts to shed further light on the pathogenesis of multiple sclerosis the whole field of "demyelinative" diseases has again been surveyed. The lesions, comparison of clinical features and the known facts of etiology of the "demyelinative" diseases in man on the one hand, and the nature of the pathologic process in the experimentally induced demyelinative encephalopathies in animals on the other, have been subjected to further analysis. As a result of detailed analysis of the morbid anatomy of spontaneously occurring human disease, renewed emphasis has been placed on concepts previously proposed solely on the basis of analogies to experimentally induced hyperergic tissue reactions in animal brains.

The practitioner will be disappointed to find no section providing him with an outline of therapy which he can use with the expectation of predictable benefit in treating multiple sclerosis. This apparent omission has its reasons. It would appear highly unlikely that any therapy will ever be successful in reversing the permanent damage and gliosis of nervous tissue present in the later stages of multiple sclerosis. Here only symptomatic help from physical therapy, rehabilitative technics and a few palliative drugs can be offered. The importance of such measures in adding to the well-being and useful life of the crippled patient with multiple sclerosis is now established. The interested physician can easily inform himself concerning this aspect of management by reading the manual on this subject distributed by the National Multiple Sclerosis Society.[1]

But what of the treatment for the earlier and reversible stages of multiple sclerosis? The unpredictable course of the disease, with spontaneous remissions even from serious degrees of involvement, has made evaluation of any specific treatment almost impossible. The many reports of various therapies alleged to benefit the disease have not been included in this Symposium since in most instances they lack adequate confirmation. It may be said that no method has succeeded in curing the disease nor in producing lasting improvement which could be shown to be the specific result of the treatment used. Mass methods in some treatment centers have unfortunately influenced patients who happened to have coincident remissions, and their physicians, to express unwarranted and unjustified enthusiasm. For the practitioner who wishes to leave no stone unturned in his therapeutic approach to the present patient with multiple sclerosis and who is desirous of applying any potentially valuable but unsubstantiated specific method of therapy, reference is made to previous reviews of treatment, one of which is also distributed in manual form by the National Multiple Sclerosis Society.[2]

Throughout the contributions in this issue many allusions are made to possible factors of causation of multiple sclerosis. Precipitating factors, links in the chain of causation, mechanisms and fundamental reactions remain intertwined, and their clear relationships to each other incompletely elucidated. However, a great array of facts based on careful scientific study both in the clinic and laboratory is presented. It is these facts that ultimately will form the foundation for an intelligent approach to what in the end is the goal of most medical research—the successful treatment of the disease.

GEORGE A. SCHUMACHER, M.D.
University of Vermont
Burlington, Vt.

[1] GORDON, E. E. Multiple Sclerosis: Application of Rehabilitative Technics. New York, 1951. National Multiple Sclerosis Society.

[2] SCHUMACHER, G. A. Multiple sclerosis and its treatment. *J. A. M. A.*, 143: 1059, 1140, 1241, 1950.

Symposium on Multiple Sclerosis and Demyelinating Diseases

Multiple Sclerosis—The Clinical Problem*

D. DENNY-BROWN, M.D.
Boston, Massachusetts

MULTIPLE sclerosis presents the threat of severe disablement with an additional urgency derived from its acuteness of onset in young, otherwise healthy people. So striking a deviation of health demands an explanation that is not easily provided. There are two chief sources of difficulty: The first is the present inability to estimate the disease in life by any means other than the neurologic disorder it produces. The second is the lack of understanding of its pathogenesis. We can assess the presence or absence of activity of the disease process only by reference to the past history of the presenting signs. We can advise regarding the future only in terms of general principles. Even in this procedure difficulty occurs because advice based on analogy of the disease with inflammation and resulting immunity conflicts with other equally firmly held beliefs founded upon conceptions of allergy and tissue hypersensitivity. In this confusion the clinician naturally holds fast to his basic approach to all disease processes, namely, the knowledge of the natural behavior of the disease, correlated with such facts as he can ascertain regarding the reaction of his particular patient. Such knowledge tends to be lost sight of in an era of enthusiastic and dramatic therapeutics, with a host of overpublicized and often conflicting claims. The present paper does not aim to summarize the many and varied contributions to knowledge of the disease, for which the reader may be referred to the earlier review by Brain,[1] the comprehensive symposium of the Association for Research in Nervous and Mental Disease[2] in 1948 and the recent extensive summary of Schumacher.[3] Rather it attempts to portray the extent of the clinical problem remaining in spite of the many interesting and valuable investigations made in recent years.

The first and most important clinical problem is diagnosis. In the beginning multiple sclerosis was separated from other similar nervous diseases by the famous Charcot triad—intention tremor, nystagmus and scanned speech. Even before Charcot's lectures Leyden and others had recognized that paraplegia resulted from the disease, and in 1889 Uthoff had described the characteristic retrobulbar neuritis. Recognition that the triad was the end result of only one type of this disease in which the brain-stem bore the brunt of the attack was, however, long delayed. Only in the 1900's was the predominantly paraplegic form of the disease recognized (Burr and McCarthy[4]). The unique importance of multiple sclerosis in the causation of unilateral retrobulbar neuritis, although recognized by Gordon[5] in 1909, was generally accepted only after Symonds[6] and Adie's[7] papers. The conception of multiple sclerosis as the cumulative result of repeated attacks, each accompanied by fresh patches of the disease, each contributing to a residue of symptoms and signs, dates from the pathologic researches of Dawson[8] and Birley and Dudgeon.[9] These made it possible to view the protean symptomatology and varied course as the logical outcome of successive crops of patches of disease with varied incidence in four chief locations: white matter of spinal cord, of brain-stem, brain and optic nerves. The distribution could be predominant in, or wholly limited to, one of these areas. The inferred sequence of pathologic change in one patch; acute myelin breakdown, cellular reaction, fatty phagocytosis, progressing to glial scar, correlated well with subacute onset of a symptom reaching maximal disturbance of function in twelve to seventy-two hours, followed by maintained disorder for two to six weeks and this by gradual return of function in the follow-

* From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School, Boston, Mass.

ing six to twelve weeks. It is clear that axis cylinders bared of myelin for a distance ceased to conduct in the acute phase of the disease, and that recovery of conduction of many fibers in the patch is responsible for the variable degree of remission. These correlations with pathology have been most obvious in short nervous tracts such as the optic nerve and brain-stem structures, and less clear in relation to damage to the spinal cord. It has been generally assumed that the long spinal tracts, more vulnerable to persistent damage by reason of passing through several patches, are more liable to ultimate interruption.

The clinician therefore translates the observed signs, in terms of the history and distribution of symptoms, into a picture of constellations of patches of central nervous disease in different phases of evolution. A fresh attack of numbness or weakness of a limb, of dizziness with diplopia, of blurring of vision, means usually a fresh patch in the dorsal or lateral column of the spinal cord, in the brain stem or in the optic pathway. Ataxia, cerebellar incoordination, nystagmus and spasticity portray the cumulative residual effects of many attacks. With such clinical principles in mind it is natural to separate from the most common types of multiple sclerosis varieties of the disease presenting, on the one hand, a rapid course with attack upon attack throughout the nervous system in a matter of weeks (acute multiple sclerosis) or, on the other, a slowly cumulative, unremitting course, usually leading to spastic paraplegia. On such principles the progressive demyelination proceeding from one focus in the cerebral hemispheres seen in Schilder's diffuse encephalopathy differs as sharply in its way from multiple sclerosis as the approximately symmetrical myelitis, sometimes with bulbar involvement, occurring in one attack ten to fourteen days after the onset of a specific fever (vaccinial encephalomyelitis, etc.). In Schilder's disease the signs of extension of a lesion from one cerebral focus to include more and more related anatomic structure gives a course more comparable with brain tumor than with multiple sclerosis. In the diffuse encephalomyelopathy of specific fevers the symmetry of the process, its time relationship with fever and absence of tendency to relapse also depart from the natural course of multiple sclerosis. The condition known as neuromyelitis optica (Devic's disease) is also set apart by its natural history. In this the close association of bilateral (though often very asymmetrical) retrobulbar neuritis with bilateral damage to the cervical spinal cord, each with subacute onset, can be more closely imitated by multiple sclerosis. Only by the absence of subsequent relapse and the density and persistence of the central scotomas can Devic's disease be set apart. The clear-cut scotoma is related to cavitation of the lesions. The value of these clinical differentiations is at present only in relation to prognosis.

Continued study of the clinical manifestations of multiple sclerosis led to its earlier recognition by means of the association of appropriate type of onset and remission with disorder in function of characteristic type and location. The onset of unilateral retrobulbar neuritis, with mistiness of vision, central or paracentral scotoma in twelve to seventy-two hours in one eye, without complete loss of vision or pupillary reaction, without change in retina or media, followed by gradual recovery of excellent vision in approximately two to eight weeks, has no ready explanation except in terms of multiple sclerosis. The early supposition that such a disorder can be due to sinus disease has long been exploded.[7,10] In the same manner, but with less certainty, the onset of a numbness and uselessness of one arm, or one leg, with signs chiefly or only related to damage to the dorsal column of the spinal cord, appearing and remitting at a rate comparable to that of retrobulbar neuritis has also a high probability of multiple sclerosis even if no evidence of multiplicity of lesion is present. There are more possible causes of unilateral and bilateral corticospinal tract damage or of cranial nerve palsy; but if the mode of evolution and remission of the disorder correlates with the typical behavior of the patch of multiple sclerosis and if other causes can be excluded by examination of spinal fluid and x-rays, there is a clear presumption of multiple sclerosis. Nevertheless, the diagnosis still remains presumptive until the appearance of another focus confirms the original impression.

Of course, the clinical diagnosis takes many other facts into account. The age of the patient is important; an onset before the age of sixteen years or after the age of 45 years is open to great suspicion. The occurrence of muscular atrophy, loss of deep pain sensation, of segmental pain for example, immediately questions the conclusion. Yet all these may occur in multiple sclerosis, their atypical characteristics being ultimately outweighed by the multiplicity and

course of other signs. Even homonymous hemianopia, aphasia or epilepsy may be due to the disease. The old observation that onset of the disease after the age of thirty is more likely to lead to paraplegic disorder with little or no remission is fully borne out by the recent careful analysis of Müller[11] who, in addition, finds good statistical basis for more rapid relapses after the age of twenty-five. At any age the typical remission may fail to occur owing to the extent of the initial patch of disease or to obscuration by further lesions. In the absence of multiplicity of lesions and of clear remission the diagnosis remains uncertain and, failing confirmation from laboratory studies, is likely to remain so until further signs develop. Until some reliable measure of the disease is available the diagnosis of multiple sclerosis will continue to exercise the art of clinical observation.

LABORATORY TESTS

The only laboratory findings of clinical utility are in the spinal fluid. It is estimated[12] that 58 per cent of patients with multiple sclerosis present abnormal colloidal gold sol curves, varying from strong first zone paretic response to a mid-zone curve of doubtful significance. Indeed, it has been said that a paretic gold curve with negative Wassermann reaction is pathognomonic of multiple sclerosis. Although this is not entirely true, the evidence may at times help the clinician to reach a conclusion in doubtful cases. The zinc precipitation of gamma globulin (Donovan, Foley and Maloney[13]) runs closely parallel to the gold curve and has the same significance, but is more simply quantitated. A positive Pandy (globulin) test is a more coarse criterion. The gamma globulins responsible for these reactions are not specifically related to multiple sclerosis and occur in other diseases of the nervous system.[14]

An elevated cell count is found in 35 per cent of cases.[12] The reaction, if any, is lymphocytic, and is commonly present in the acute stage of retrobulbar neuritis. It may occur with other forms in association with recent activity. The presence of more than 50 cells in the spinal fluid is in fact a warning of other possible cause although cell counts as high as 115 have been recorded.[15] These abnormalities arise early in the acute phase and persist long into the clinical remission. Unfortunately for diagnostic purposes their degree correlates largely with the extent of recent disease, so that they give clearest answer in those cases in which clinical evidence is also likely to be conclusive. In the very slowly progressive forms or when disorder of function is early and isolated, they are seldom of assistance. The blood count and blood clotting mechanism are unaffected. The serum globulins show no change.[12] The spinal fluid changes reflect only the tissue reaction in the neuraxis, and there is no present evidence of underlying systemic abnormality.

There is no evidence of change in vital signs, in immunity reactions, in sedimentation rate, in blood coagulation or other common evidence of chronic inflammatory disease.

COURSE OF THE DISEASE

In an excellent study of forty-six cases of multiple sclerosis proven by autopsy, Carter, Sciarra and Merritt[16] reported durations varying from six weeks to sixty-four years before death, with average duration from time of onset of approximately thirteen years. Such material, however, is selective in several respects and the average expectation of life is closer to twenty-seven years,[11] but this figure gives too great an emphasis on patients showing a progressive paraplegia from the onset. The statistics of Lazarte[18] are more typical of office practice because he found, for example, that of patients who were ambulatory when first seen and traced eleven to sixteen years later, 29 per cent had died, 18 per cent were helpless, 10 per cent partially helpless and 43 per cent remained ambulatory. Thirty-four per cent were still able to work after this period. Such statistics in a variable disease still fail to portray the fate of the survivors. From my own case records from a hospital for chronic nervous diseases I can provide the obverse side to autopsy statistics in the form of case records of twenty-six patients over fifty years of age (including twelve over sixty), in whom the average duration of undoubted multiple sclerosis was twenty-six years, and the average duration of disablement thirteen years. In ten of these patients there had been no sign of activity of the disease in the last ten years of observation whereas in six there had been renewed symptoms and signs within two years. Eleven patients had had the disease for over thirty years, one for fifty-eight years. The longest remission was thirty-six years (onset at the age of twenty, absence of attacks between the ages of thirty and sixty-six, then renewed attacks and persistent disability). Even

this picture fails to take full account of the survivors. I can vouch for two patients, one a woman aged seventy-nine and still living, the other a man who died aged seventy-four of heart failure, each of whom had more than one bout of undoubted multiple sclerosis between the ages of twenty and twenty-four, which left the woman with a mild spastic paraplegia and intention tremor (able to walk with a cane) and the man with a mild dysarthria, intention tremor and spastic monoplegia, both without any further activity of the disease for the remainder of their lives. The course in such cases is greatly at variance with the usual textbook description yet has been noted by others, for example, Bramwell[19] and McIntyre and McIntyre.[20]

The prognosis on the whole is better than many would have us believe. If the acute form of the disease, with rapidly progressive course leading to severe paralysis within the first six months, is set aside as having a grave prognosis, and that presenting poor remissions (particularly in terms of paraplegia) is regarded as having a poor prognosis, there remain more than a half, perhaps two-thirds in some communities, in whom the disease will run a mild course. The ultimate disablement is almost always a spastic paraplegia, usually with troublesome spasms in flexion, but some will escape this fate. MacLean et al.,[21] analyzing the disease in a small rural community, concluded that disability mounted at the rate of approximately only 4 per cent per year. Although such disability is surely a medical problem, it should not be allowed to panic the patient and his family into heroic but ill advised therapy and expenditure.

It is evident that the problem of the clinician faced with multiple sclerosis is exactly comparable to that of pulmonary tuberculosis before the days of Koch and Roentgen. He is aware that the course of the disease varies greatly, that there is a natural tendency to remission, and he seeks to determine those factors which favor remission and those which precipitate relapse. Some degree of natural remission from the most recent attack is almost certain. In less than one-fifth of cases in their first attack is remission so slight as to be of no consequence, or overshadowed by further progression of the disease. Since multiple sclerosis advances characteristically by the occurrence of wave upon wave of attacks, the most pressing problem is the prevention of further attacks. The known precipitants are few and some will question the validity of any. An infection of any kind, a general anesthetic, pregnancy and overfatigue are those most generally agreed upon. The presence of fever for a few days prior to relapse, during or immediately following, for example, a streptococcal sore throat, a common cold or an infected sinus, is too striking to be overlooked. Yet this occurs in only 5 per cent of cases. No single organism has been regularly implicated. Surgical operation is also frequently followed by relapse, regardless of the nature of the surgery; hence general anesthesia is regarded as hazardous. No particular anesthetic has been implicated, but spinal anesthesia is regarded as having special dangers. Likewise pregnancy is associated with relapse in 40 per cent of women with multiple sclerosis. The relapse, however, may occur during the pregnancy or in the puerperium, in haphazard and uncertain relationship. Tillman[22] has estimated that whereas onset of the disease during pregnancy occurred in only one in 31,000 deliveries, fifty-two patients suffering from multiple sclerosis had twenty-eight fresh episodes in seventy pregnancies (six during pregnancy, twenty-six in puerperium). Four patients had a remission begin during pregnancy.

None of these precipitants of relapse is regularly found. Their common factor is a lowering of general health and well being. That this is an important factor is seen in the equally common precipitation of relapse after a long remission by a period of intense overwork and poor sleep. In a more general sense the importance of this is reflected in the common finding among practicing neurologists that many well-to-do patients who have led a life of comparative ease, especially with frequent sojourn in a warm climate, have managed to maintain remissions of twenty, even forty years, after more than one early attack. Both patients I have cited as living to over seventy-four without further attack were in this fortunate position. This is in striking contrast to the usual course in the city clerk or laborer who returns to work soon after leaving the hospital. This has long influenced my own advice to patients. Freeman[23] has written convincingly upon the same theme. The author believes that sanatorium treatment of multiple sclerosis is as great a need as it is for tuberculosis. Weaknesses of such a plea are the absence of evidence of infectivity, and the

inability to demonstrate that remission depends on a serologic immunity, but the evidence is as strong as it was in 1900 that rest and fresh air could build immunity to tuberculosis. Certainly in the first three weeks of an attack rest hastens the onset of remission and probably increases its degree more than any known therapeutic agent given to ambulatory patients in the same stage.

The consistency of the course of the disease in any individual patient is more striking than the factors which influence it. I have records of a patient in whom nineteen attacks had occurred in the course of ten years, yet leaving only the most mild reflex changes, nystagmus and temporal pallor in the optic discs. The longest interval of freedom from attack had been approximately ten months. Symptoms had persisted for intervals of seven days to six weeks, but recovery had been progressively and subjectively complete after each attack. Usually no medical treatment had been given. At the other end of the scale is acute disseminated sclerosis. In such a case, in a girl of twenty-three years of age weakness of the lower limbs with diplopia and blurred vision progressed to stupor, coma and death in four weeks, with large and numerous fresh patches of the disease demonstrated at autopsy. The degree of remission appears to depend upon the size of the individual patches of demyelination as much as the frequency of their occurrence. Although multiple sclerosis, in the sense of the relapsing-remitting syndromes of characteristic distribution familiar to the clinician, undoubtedly belongs to a whole class of demyelinating diseases, the histology of each patch of the disease is surprisingly uniform from case to case of multiple sclerosis. Less complete demyelination of the patches, so-called "shadow patches," may reflect a less intense pathogenic activity but such patches do not correlate with a generally mild clinical course, just as cavitation and necrosis are not found in the severe and vicious forms of the disease except as pathologic curiosities. The most common finding in cases of multiple sclerosis of truly mild course has been smallness of the individual patches of the disease, a finding which indicates a resistance to its onset rather than perfection of the recovery process.

Multiple sclerosis occurs in more than one member of a family in 6.5 per cent of cases according to a recent study by Pratt, Compston and McAlpine.[24] It is extremely rare for more than two members of one family to be affected although the disease has been reported in three generations. It is extremely rare for two patients living in the same household to contract the disease. A very particular personal liability is manifestly more important than any infection or exogenous intoxication. The recent discovery of the experimental hypersensitivity reactions of the nervous system appeal to the clinician because such special tissue reactions explain the distribution and case incidence better than any infective process. Yet the known hypersensitivity reactions of the human nervous system, of which the "neuroparalytic accident" of rabies inoculation is the best example, do not in fact resemble multiple sclerosis. Studies of allergy in multiple sclerosis give no clear correlation. The haphazard asymmetrical patches of the disease appear to make any circulating biochemical intoxication unlikely. Excepting Leber's hereditary optic atrophy, multiple sclerosis stands apart from all the degenerative diseases of the nervous system by virtue of its asymmetrical distribution and intermittent course.

The nature and course of multiple sclerosis are baffling in their many uncertainties and suggestive affiliations, yet the natural history of the disease is not entirely erratic. The remitting course is not only its most prominent diagnostic feature but also its chief prognostic index. The most effective therapy would be the prevention of relapse.

PSYCHIATRIC DISORDERS

No physician who has handled multiple sclerosis can fail to be impressed by the remarkable personality change that is associated with the disease. The most prominent feature is euphoria, which has been commented upon since the time of Charcot. Wilson and Cotterell[25] in a penetrating analysis distinguish a eutonia as well as euphoria—a prevailing sense of well being as well as emphasis on the pleasant versus the unpleasant side of every incident. The rarity of hallucinosis, delusions, excitement and dementia are generally recognized. Yet, few have noted the lack of responsibility, the poor judgment and the poverty of memory which very gradually become evident in progressive forms of the disease. It is only recently, with the appreciation of the effects of frontal lobotomy, that the failure of the patient to appreciate the gravity of a situation, especially when it concerns themselves, has become significant. Braceland and Giffin[26] relate the case of a young

woman with severe obsessive compulsion neurosis which vanished with the onset of multiple sclerosis. In such respects the present author would liken the effect of cerebral multiple sclerosis to that of lobotomy. The equanimity with which future disaster or discomfort can be faced is a frontal lobe sign, and in multiple sclerosis is combined with that facility of emotional display which is characteristic of mild pseudobulbar syndromes. Failures in judgment, evident in such obvious features as concern over minor paresthesias while disregarding disabling symptoms, are common. Memory defect is a symptom only of gross disorder. If those characteristics are held in mind, the peculiar features of the psychiatry of multiple sclerosis are as distinct as those of general paresis. Indeed, in the primarily cerebral form of the disease multiple sclerosis may greatly resemble general paresis, except for the preservation of memory function.

Some years ago the primarily psychiatric type of multiple sclerosis used to be commonly confused with neurasthenia, by which was meant the combination of querulous personality with easy fatiguability. In some patients frankly hysterical symptoms may characterize the early stages of the disease.[1,27] Such symptoms are easily removed by countersuggestion. The author believes that hysteria of this type arises from loss of judgment which itself may not be obvious at that stage. The absence of abdominal reflexes in such cases was emphasized as an important sign. We would now change the emphasis. Fatiguability and absent abdominal reflexes are non-specific signs, of themselves of no diagnostic value. We stress the combination of moria, failure of judgment and euphoric emotional lability in association with exaggerated tendon reflexes, and preferably abnormal plantar responses or Hoffmann's sign. Such cases can be treated only on the general principles used in the management of other types of the disease. It should be hardly necessary to say that electroshock or lobotomy are unlikely to correct a condition so closely resembling their own effects.

In recent years the number of patients obsessed with fears of multiple sclerosis, themselves suffering from an early stage of the disease, has become noticeably increased. The author is convinced that this phenomenon derives entirely from unwise publicity of the problems of multiple sclerosis. Euphoria will ultimately reverse this symptom but until this happens it can be extremely troublesome for all concerned.

PROBLEMS IN MANAGEMENT

As with many other chronic diseases the function of the physician does not end with the statement that there is no treatment known to affect the course of multiple sclerosis. He must be able not only to offer intelligent judgment regarding the trial of one or other of innumerable therapies, which attain a seasonal popularity and of which the number alone bespeaks doubtful utility, but he is in addition expected to advise regarding many questions as to the extent of exertion advisable, ability for occupation and a host of other possible adverse or adjuvant, physical and mental factors. For this to be done effectively it is essential that the physician have a clear idea in his own mind as to the degree of incapacity, the extent to which this is due to recent activity of the disease and the frequency and duration of relapses in the recent past. To adopt a uniform attitude to multiple sclerosis is comparable to giving the same prognosis and treatment in all arthritis or nephritis, regardless of type.

Many have emphasized the undesirability of allowing the patient to know the name of his disease, preferring to hide behind such euphemisms as "myelitis," "inflammation of the nerves," etc. The patient in time inevitably learns the name of his complaint, often in a manner which conveys unnecessarily gloomy implications, and then immediately loses confidence in the advisers who well meaningly connived to conceal the truth. The truth in fact is seldom as bad as the fund-raising campaigns state. Indeed, the older textbooks err in failing to stress the long average survival, the high frequency of remissions and consequent continuance of occupation. The patient deserves to be protected against statements that multiple sclerosis is a progressive disease which rapidly and inevitably leads to a wheel-chair existence. It is the duty of the physician to emphasize that the patient will not necessarily be totally disabled, as much as if the statement were made regarding an osteoarthritic hip joint. The same categorical view of multiple sclerosis is responsible for the uncompromising attitude taken by many business concerns to knowledge of the diagnosis of multiple sclerosis in an employee. Of many such cases I may cite that of an executive with many years service in a large shipping

concern who, at the age of fifty-two, had a mild spastic weakness of one leg which had remained an unchanging residue of two undoubted attacks of multiple sclerosis at the ages of twenty-nine and thirty-one. No further attacks had occurred or were indeed likely after so long a remission. Yet at fifty-two in the course of routine check-up of all employees the correct diagnosis was made. The man was promptly relieved of his position and retired by the company, who refused to reconsider their decision even when the true facts were independently presented to them. Such cases are not uncommon. The abolition of such injustice will not be obtained by further concealment of the truth but by better appreciation of the nature of the disease.

More harm is done by failure to acknowledge uncertainty than by omission of trial of the latest scientific nostrum. It can confidently be said that more patients suffer from delayed recognition of spinal tumor, acoustic neuroma, prolapsed cervical disc and such similar conditions, owing to tenacious adherence to an earlier presumptive diagnosis of multiple sclerosis, than are cured by any of the much publicized treatments claimed for this disease. The error here is not in the initial doubt in diagnosis but in the failure to indicate its need for revision at a later date. This precaution is particularly necessary when a disease process has exhibited remission and relapse, with each attack pointing to damage of the same small area of the nervous system, for example, the same region of cervical spinal cord. This is not the natural behavior of multiple sclerosis.

In a disease in which simple bed rest so commonly secures a remission of symptoms, the omission of such rest for the first three to four weeks appears difficult to justify. After that time graduated resumption of activity may be allowed according to the degree of remission of symptoms and signs. Since no particular activity is harmful, none need be proscribed, but fatigue is uniformly to be avoided. This means that the patient may ultimately undertake any exertion within reason, provided he begins gradually and remains within the limits of excessive fatigue. As weeks and months pass he may be allowed to attempt more and more. Any exact period is purely arbitrary, in regard to any hazard, but the same principle has led the author to advise against pregnancy, for example, until at least two years have passed since the last new symptom.

When relapse has been recent, the administration of any substance which provokes a general reaction is liable to provoke further relapse. This caution is not a myth. Soon after the discovery of the effect of fever on general paresis, malaria and hot-box were tried on multiple sclerosis.[28] The effect was seldom beneficial and sometimes disastrous, as in a patient in whom bulbar signs recurred in increasing severity with each bout of malaria until the treatment was stopped. For a number of years a course of "protein shock" by means of injections of typhoid vaccine was regularly used in chronic stationary cases, but the risks of its use shortly after a relapse of the disease were well recognized. The procedure, or the febrile reaction associated with it, then tended to precipitate further relapse. I have been recently informed by a competent neurologist of a patient with recent retrobulbar neuritis whose vision was remarkably improved by the administration of cortisone, but in whom blindness immediately supervened when administration of cortisone was stopped. No doubt, ways of minimizing such calamities will be found but all should be aware that the danger exists. We have for this reason been opposed to the use of histamine. We have been impressed more by the dangers of giving enough dicoumarin to change blood clotting than by its effect on multiple sclerosis. ACTH and cortisone influence the tissue reaction of multiple sclerosis in the same manner that these substances change other types of tissue reaction, but the possible severity of renewal of symptoms when administration is ceased makes their use in the acute stage of the disease extremely hazardous. In the chronic stage the usefulness of all these substances is dubious. Here then is the most difficult dilemma of multiple sclerosis. If remission has not occurred within an expected time, or if further relapse occurs, should such potent therapy be used? It is not possible to la down uniform rules of procedure. Each case must be judged independently, but it should be emphasized that the acute phase of the disease can be as easily provoked to further relapse as to remit. General anesthesia, overexertion and fever are particularly to be avoided. The real test of treatment is the rapidly progressive unremitting form of the disease, and in such cases the author has been disappointed in all the remedies advocated to date.

There is no known potent dietary factor. The disease is rare in warm climates but the chief reason for advising a warm, dry climate is the avoidance of chills, colds and sinusitis which are frequently associated with relapse. The general use of vitamins and liver extract has no basis in deficiency of factors contained in these. Rather they have replaced arsenic as the stimulator of appetite and well being. Any measure which can be justified on the grounds of improving general health, if health is indeed not perfect, is advisable. We find no special reason to recommend B_{12} and prefer liver extract for this purpose.

In the chronic, stationary stage of the disease the chief problem is to enable the patient to make the most of his remaining resources. Spasticity and ataxia, whether produced by multiple sclerosis or by other diseases, are greatly influenced by the emotional state of the patient and by continued exercise. Reeducation of such patients in walking is not new, although the more general training of physical therapists in such rehabilitation and recent publications, such as that of Gordon,[29] sponsored and distributed by the National Multiple Sclerosis Society, are excellent. In the chronic stage it is essential first to assess the degree of disability in relation to the magnitude of physical signs. It is important to emphasize, for example, that extensor plantar responses alone, or loss of position sense in the toes alone, do not account for inability to walk. How much does loss of confidence, careless correction of incoordination or unwarranted anxiety account for poor performance? The answer to these questions will often indicate discrepancies of large significance for the care and even employment of the patient. Reeducation and encouragement in exercises have achieved lasting results far superior to any drugs in these respects. So far no medicines have been claimed to influence the flexion spasms, dysuria and ataxia, which are the truly difficult problems of the chronic stage of the disease.

SUMMARY

Although multiple sclerosis has pathologic and probably etiologic affiliations with a whole group of demyelinating diseases, its intermittent and asymmetrical clinical symptomatology is highly characteristic. The natural tendency to remission is very considerable and disability may be long deferred. Patients with a fair prognosis are too often discouraged, lose employment and led to try expensive and heroic cures, at the same time disregarding simple measures of known value. The psychiatric symptoms are sometimes mistakenly treated, particularly when they are early and prominent. In the acute stage of onset or relapse harm can be done by too energetic measures. Promotion of general health is more important than specific therapy. A better understanding by internists of the problems of the disease, particularly in relation to the presence or absence of recent relapse, and in the recognition of favorable and unfavorable prognosis, would avoid much unnecessary therapy. When diagnosis is unavoidably uncertain, the possible presence of other disease must continually be borne in mind.

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The Morbid Anatomy of the Demyelinative Diseases*

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It has long been the practice to set apart a group of diseases in which demyelination is a prominent feature. They are believed to possess characteristics that point to a unique etiology and pathogenesis, as yet unknown. To state these characteristics in an exact definition is, however, difficult if not impossible. Neuropathologists pretend to know what a demyelinative disease is, yet have found it hard to describe in a few simple words. The actual source of this difficulty, in the opinion of the present writers, is that there probably is no disease in which myelin destruction is the primary or exclusive pathologic change. The whole idea of a demyelinative disease is more or less of an abstraction which serves merely to focus attention on one of the more striking and distinctive features of a pathologic process.

The commonly accepted criteria of a demyelinative disease are: (1) destruction of the myelin sheaths of the nerve fibers; (2) relative sparing of the other elements of nervous tissue, i.e., axis cylinders, nerve cells and supporting structures and (3) a distribution of lesions, often perivenous, either in multiple, disseminated foci throughout the brain and spinal cord or in single foci spreading from one or more centers. This last attribute, which is not explicit in most definitions, is nonetheless shared by all the generally accepted members of this group of diseases. Another peculiarity, which applies particularly to multiple sclerosis, is the lack of secondary or Wallerian degeneration in the affected fiber tracts, but this is only an expression of the relative integrity of the axis cylinders in the lesions.

The diseases included in the following classification conform approximately to the above criteria. Like all classifications except those based on etiology, this one has its faults in being somewhat arbitrary and not entirely consistent. In most of the diseases that are here classified as demyelinative, degeneration of both myelin sheaths and axis cylinders and even necrosis of tissue may occur. Furthermore, a number of diseases in which demyelination is a prominent feature are not included. For example in some cases of anoxic encephalopathy the myelin sheaths of the radiating nerve fibers in the deep layers of the cerebral cortex or in ill defined patches in the convolutional and central white matter are destroyed while most of the axis cylinders escape serious injury. A selective degeneration of myelin may also occur in some small, ischemic foci due to vascular occlusion, and in diphtheritic polyneuritis there is a demyelinative lesion of the spinal roots, nerves and spinal ganglia. Also, in subacute combined degeneration of the brain and spinal cord associated with pernicious anemia myelin may be affected more than axis cylinders. These conditions and some others are excluded from the classification presumably because their etiology is known and they exhibit pathologic features which are judged to be more fundamental than the demyelination.

In the language of neurology the term demyelination has, then, acquired a special meaning; and if it is to retain its value, it should be used in this restricted sense and not as a synonym for complete degeneration of nerve fibers or necrosis of nervous tissue, even though in a section stained for myelin the lesions may look alike. In this latter, more general sense there are few diseases of the central nervous system to which the term would not apply.

CLASSIFICATION OF THE DEMYELINATIVE DISEASES

A. Multiple Sclerosis (also Disseminated or Insular Sclerosis)
   1. Chronic relapsing encephalomyelopathic form
   2. Acute multiple sclerosis

* From the Neurological Service, Massachusetts General Hospital and the Department of Neurology, Harvard Medical School, Boston, Mass. This study was aided by a Grant from the National Multiple Sclerosis Society.

B. Acute Disseminated Encephalomyelitis
   1. Measles, smallpox, chickenpox, mumps (rarely) and "influenzal" encephalomyelitis
   2. Rabies vaccine and smallpox vaccine encephalomyelitis

C. Cerebral Sclerosis of the Demyelinative Type
   1. Schilder's encephalitis periaxialis diffusa
   2. Metachromatic leucoencephalopathy

D. Acute and Subacute Necrotizing Hemorrhagic Encephalomyelopathy
   1. Acute encephalopathic form (hemorrhagic leucoencephalitis of Hurst)
   2. Acute and ? subacute necrotic myelopathy

(?) Acute hemorrhagic encephalitis (acute brain purpura or acute pericapillary encephalorrhagia)

The above classification is based entirely on morbid anatomy and does not permit subdivision according to the localization of the disease processes. Although in most of these diseases there is a tendency for the changes to be disseminated throughout the brain and spinal cord, in some they may be restricted to only one part of the neuraxis. Thus the spinal cord alone may be involved in all of these diseases except the demyelinative forms of cerebral sclerosis, or the spinal cord and optic nerves may bear the brunt of the disorder, as in "optic neuromyelitis."

A. MULTIPLE SCLEROSIS

The first descriptions of multiple sclerosis were those of Cruveilhier (1835) and Carswell (1838) who referred to the gray degeneration and induration of the nervous tissue but early knowledge of the morbid anatomy came largely from the writings of Frerichs (1849), Rokitansky (1850), Valentiner (1856), Leyden (1863), Rindfleisch (1863) and Zender (1870). Charcot (1870) provided the first well-rounded exposition of the clinical and pathologic aspects of the disease and this is available in the English translation of his lectures.[9] In the past fifty years surprisingly little has been written on the pathology. The fine monograph by Dawson[13] deserves special mention. Two of the more recent reports are to be found in the Proceedings of the Association for Research in Nervous and Mental Diseases by Hassin[27] and by Zimmerman and Netzky.[55] Many of the current publications dealing with pathology have had as their main purpose the documentation of some theory concerning the etiology and pathogenesis of the disease.

The following account of the morbid anatomy is based on the study of material from approximately fifteen cases of multiple sclerosis examined in the Neuropathology Laboratories of the Massachusetts General and the Boston City Hospitals. Because pathology divorced from clinical data loses much of its meaning, the clinical abstracts of a few cases are given.

Illustrative Cases

Case 1 (MGH-5982), a male was twenty-eight years of age.* Symptoms began with slight ptosis of left upper eyelid, followed in rapid succession by impaired vision, ataxia, inability to walk, drowsiness and stupor. Additional neurologic findings were small pupils reacting slightly to light, bilateral ptosis, paralysis of both internal rectus eye muscles and some limitation of all ocular movements, and bilateral Babinski signs. Symptoms progressed steadily until death which occurred six weeks after the onset of illness. Sectioning of the fresh brain disclosed pinkish-gray areas measuring up to 3 cm. in diameter in the lenticular nuclei, optic thalami and mid-brain. In microscopic sections the myelin in these areas was destroyed and the axis cylinders were preserved, and there were large numbers of fatty macrophages. Some of the demyelinated foci surrounded small veins or were situated beneath the pia. (Fig. 5B.) There were marked perivenous infiltrations with lymphocytes and plasma cells and an infiltration of the pia-arachnoid with mononuclear cells. (Fig. 13A.) No lesions were found in the spinal cord, medulla, cerebellum or cerebral cortex and white matter.

Comment. This case is an example of acute multiple sclerosis, so diagnosed because of the large asymmetrical patches of demyelination in the brain stem in which few axis cylinders and none of the nerve cells were destroyed. The restriction of the lesions to the basal ganglia, midbrain and pons with no involvement of the cerebral white matter, cerebellum, medulla or spinal cord is unusual. The perivascular infiltration was unusually pronounced and the relation of the lesions to small veins was striking, par-

* All of the ages given in these illustrative cases were taken at the time of death and not at any one time during the illness.

ticularly along the margins of the larger lesions as shown in Fig. 5B.

Case 2 (MGH-7994), a male, was sixty-two years of age. At the age of thirty-three the patient began to complain of a queer feeling in his head and was later committed to a psychiatric hospital. Three years later he was "silly and overactive." At the age of thirty-nine slurring of speech, unsteady gait, ataxia of arms and legs, spasticity of legs and extensor plantar reflex on the left, were noted. Death occurred twenty-three years after onset of neurologic symptoms. On sectioning the brain there were sharply defined, pink-gray foci 0.5 to 3.0 cm. in diameter in the white matter near ventricles, and a number of smaller lesions in the mid-brain and medulla. On microscopic examination of the lesions the myelin was destroyed and the axis cylinders, though plentiful, were diminished in number. There was a pronounced fibrous gliosis; microglial cells were few in number and macrophages conspicuously absent. Slight lymphocytic infiltration was observed around a single vessel. The spinal cord was normal on gross and microscopic examination.

Comment. In contrast to the first case this is an example of the chronic form of multiple sclerosis in which symptoms had been present at least twenty-three years. The involvement was unusually slight and there were no recent lesions or indications of active disease at the time of death. Also, the case is unusual in that the spinal cord did not appear to be involved. An extensor plantar reflex was noted only on one side, opposite a lesion in the inferior olive and pyramidal tract.

Case 3 (BCH-NP 48-4) a female, age thirty-three years, had an attack of retrobulbar neuritis. This improved after some weeks and was followed by recurrence, first in the right and then the left eye. She later developed paraplegia and sensory impairment in trunk and legs. Partial recovery took place but her legs remained weak and useless until her death nine months later. On sectioning of the spinal cord a small cavity at T_5 level (Fig. 8B) replaced the central and posterior gray matter on one side where there was also degeneration of myelin in the lateral and anterior columns. In other segments there were circumscript foci in which only the myelin had been destroyed. Microscopic sections showed demyelination in the right optic nerve (Fig. 8A), with preservation of a majority of the axis cylinders and with numerous fatty macrophages and abnormal astrocytes. There were no lesions in the cerebrum or brain stem.

Comment. Although this was a case which clinically had taken the form of "optic neuromyelitis," there can be little doubt about the diagnosis of multiple sclerosis. The lesions in the optic nerve and all but one of the lesions in the spinal cord were demyelinative. The case is unusual because of the restricted localization of the disease process and the combination of demyelinative and necrotizing lesions.

Case 4 (BCH-A49-708), a colored female, age thirty-one years, was six months pregnant and debilitated from pernicious vomiting when there was acute onset of pain and tightness in the right arm, numbness and paralysis of both arms and the left leg, and urinary retention. Cesarean section was performed. A few weeks later a nearly complete quadriplegia and burning pain in the right shoulder and upper thorax developed. After another month diplopia and nystagmus were noted and about six weeks thereafter retrobulbar neuritis, first in the right and then in the left eye. Vision and power of the limbs improved but the patient remained bedfast. Death from fibrocaseous pulmonary tuberculosis occurred fourteen months after onset of neurologic symptoms. There were several gray foci of demyelination in the pons, medulla and spinal cord but only one in the cerebrum, in the corpus callosum. The lesions were 0.2 to 0.5 cm. in diameter, of irregular shape and several were found adjacent to or around small veins. In some of the demyelinated lesions axis cylinders were preserved and others were in the form of fenestrated cavities. (Fig. 10B.) All the myelinated fibers and most of the axis cylinders in the right optic nerve were destroyed. Only the prechiasmal portion of the left optic nerve was available for study. It appeared to be normal.

Comment. This was clinically a case of "optic neuromyelitis." At least five separate exacerbations had occurred and there had been only slight remissions of symptoms. The pathologic findings were consistent with multiple sclerosis.

Case 5 (MGH-12437), a female, was forty years of age. At the age of twenty-nine she began to have severe pain along the ramus of the left mandible coming in sharp jabs, often provoked by laughing, sneezing or a draught of cold air. No sensory deficit was demonstrated. Diagnosis of tic doloreaux was made. Pain continued intermittently for the next six years. Between the ages of thirty-four and thirty-nine she developed

diplopia, paresthesias, weakness and stiffness of arms and legs, right facial weakness, intention tremor of both arms and scanning speech, emotional lability and dysphagia. The tendon reflexes were brisk and plantar reflexes extensor. During the last year or so confusion and forgetfulness were prominent symptoms. Death occurred at the age of forty years or eleven years after the onset of symptoms. Post-mortem examination disclosed an unusually large amount of subarachnoid fluid, atrophy of the cerebral convolutions and enlargement of the lateral and third ventricles to three or four times normal size. There were numerous lesions in the cerebral white matter, basal ganglia (Figs. 1 and 2B), mid-brain, pons, medulla and spinal cord and only a few in the cerebellum. The largest lesion, several centimeters in diameter, occupied a large part of the centrum semiovale, sparing a narrow strip of subcortical white matter. The lesions in the pons involved the entering fibers and spinal tract of the trigeminal nerves. At some levels of the medulla almost complete demyelination had occurred. There were large numbers of macrophages filled with fat, prominent perivascular cuffing with lymphocytes and macrophages and various degrees of gliosis. Death was due to bronchopneumonia.

Comment. This is a typical example of the severe, relapsing form of multiple sclerosis with numerous and extensive lesions of different ages through all parts of the spinal cord, brain stem and cerebrum. Mental symptoms and cerebral atrophy were more pronounced than usual. Tic douloureux is a not uncommon symptom in multiple sclerosis and occurred in at least two other cases, one of which had a lesion extending to the root entry zone of the trigeminal nerve. (Fig. 6A.)

Pathology of Multiple Sclerosis

On macroscopic examination the external appearance of the brain and spinal cord is usually not remarkable. Superficial lesions in the spinal cord and brain stem may often be detected by a sharply defined, slight depression of the surface, indicating some loss of substance. By passing the finger along the surface of the spinal cord a peculiar unevenness can be felt which is seldom found in any other disease. On the cut surfaces most of the lesions appear as sharply defined, slightly depressed, pinkish-gray areas, somewhat paler than normal gray matter. They stand out conspicuously against the normal white matter and are also detected without difficulty in gray matter. (Figs. 1 and 2.) The French have referred to these lesions as *plaques*, meaning patches, and this term has been adopted by some English and American writers. The gray color of the lesions is due chiefly to the loss of myelin. Very often the central portion of the lesion and sometimes all but a narrow marginal zone is pale (Fig. 2B) or may have a faint yellowish coloration. An unusual finding in one of our cases was a brownish-gray band that outlined the zone of demyelination along the course of the veins beneath the ependyma of the lateral ventricles. (Fig. 2A.)

FIG. 1. Case of chronic multiple sclerosis; section of fresh brain. The disease is unusually extensive, involving a large part of the central white matter. A narrow subcortical strip is spared in some places (*a*). The area extending forward and outward from the anterior horn of the right lateral ventricle is typical. There are smaller, sharply defined lesions in the basal ganglia and subcortical white matter and cortex. Some of the smallest ones are indicated by arrows. The pale center and gray marginal zone may be seen in many of the lesions. See Figure 2.

There is, as a rule, little indication of brain atrophy though moderate enlargement of the lateral ventricles may be found, particularly in elderly subjects who have had the disease for many years. In long-standing cases the spinal cord is diminished in size.

An accurate conception of the pathology can

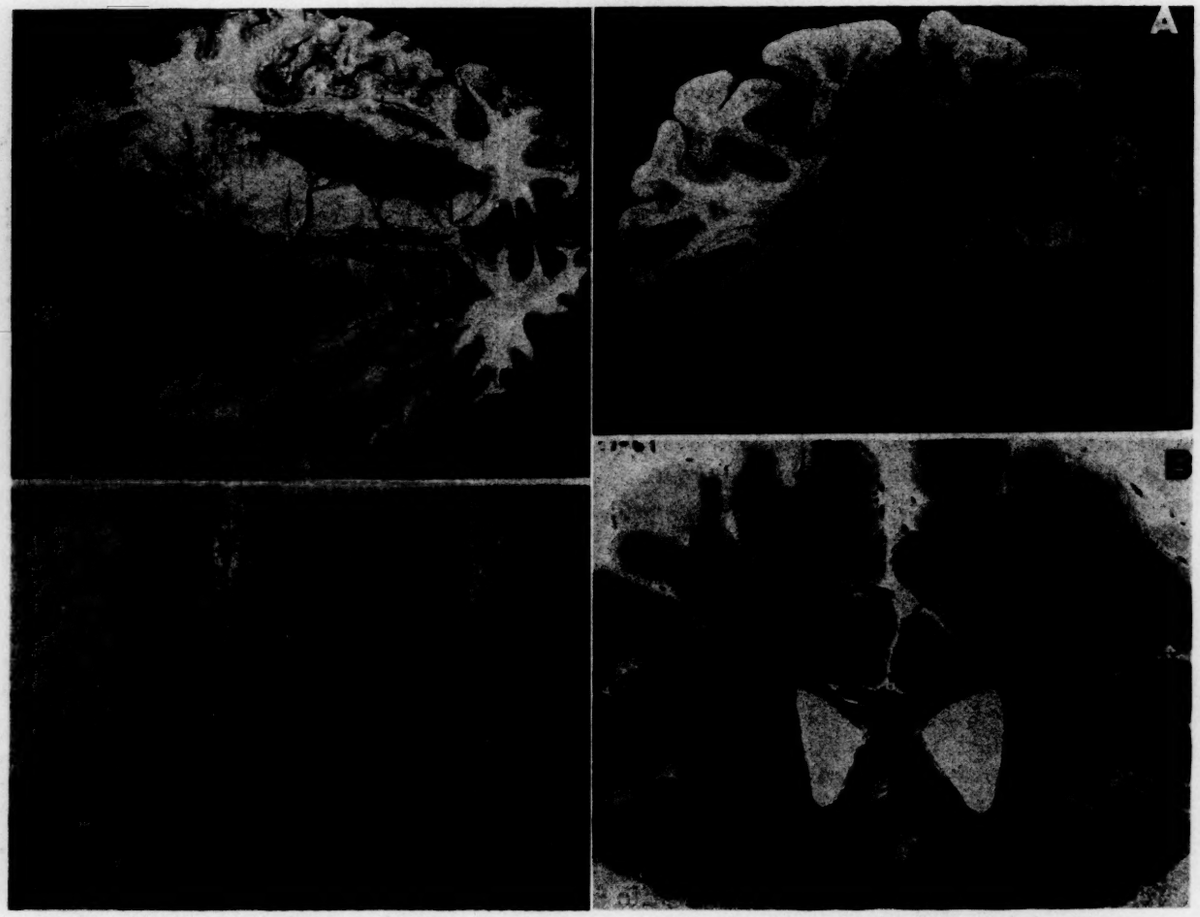

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FIG. 2. Chronic multiple sclerosis. A, ependymal surface and veins of the roof of the lateral ventricles, photographed in fresh state, showing gray zone of demyelination around some of the veins (above and to right of *a*). The large dark areas are shadows resulting from faulty lighting. B, enlarged view of a part of Figure 1.

FIG. 3. Chronic multiple sclerosis. A, coronal section through the frontal lobes after formalin fixation. The lesions appear as discrete or poorly defined patches of grayish discoloration and are particularly numerous in the central white matter. B, coronal section of frontal lobes stained for myelin. There are, in addition to the periventricular lesions, many which destroy the radiating fibers in the cerebral cortex.

be obtained only by examining the brain and spinal cord by a number of different methods, designed to bring out the changes which have taken place in the various elements of the nervous system. Although degeneration of the myelin is the most conspicuous feature of the disease, there are pronounced, equally important reactions of microglia and astrocytes and, in the early stages, an infiltration of the vascular adventitia with lymphocytes and plasma cells.

The lesions, which measure from less than 1 mm. to several cm. in diameter, are rounded or oval, and often irregular in shape. (Figs. 1 and 3A.) Usually they are sharply defined but sometimes the margin, or part of it, is indistinct and there is gradual transition from complete demyelination to normal brain tissue. Within the lesion the myelin in most instances is completely destroyed (Figs. 4 and 6) but intact myelinated fibers are sometimes found and not infrequently there is only partial demyelination consisting of an evenly distributed thinning out of the myelin sheaths ("shadow plaques"), as if the process responsible for the degeneration had not been severe enough to cause complete destruction of the myelin yet had acted with the same intensity in all parts of the region affected. (Fig. 10A.)

In most lesions there is comparatively little destruction of axis cylinders. This may be shown in two ways: (1) In silver impregnations a large proportion of the axis cylinders which are deprived of myelin sheaths are found to be intact; (2) there is, as a rule, no demonstrable

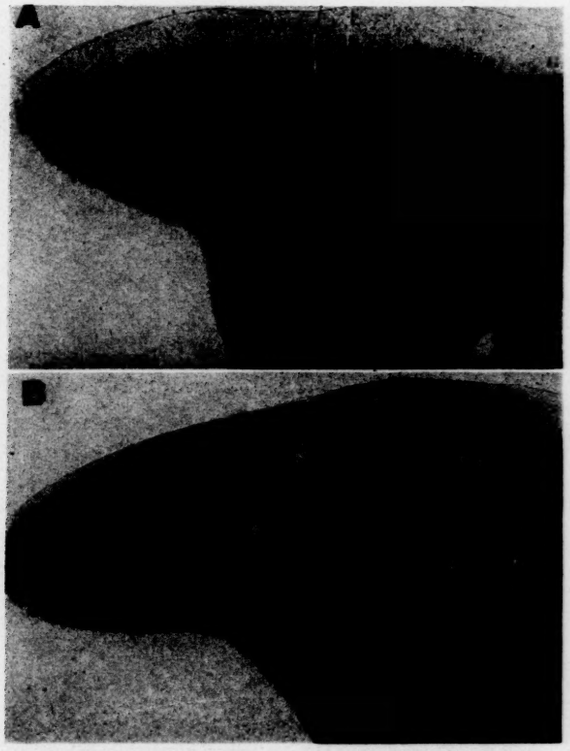


FIG. 4. Case 5. Multiple sclerosis. A, small lesion involving cerebral subcortex and cortex, stained with scarlet R and hematoxylin, showing massed macrophages in the destroyed white matter and considerably less pronounced reaction in the gray matter. Blood vessels are encircled by cuffs of macrophages. B, another level of the same lesion stained for myelin. Note absence of secondary degeneration of radial fibers of the cortex and in underlying white matter. A minute area of perivascular demyelination is seen at (*a*).

FIG. 5. Case 1. Acute multiple sclerosis. A, section of brain stem stained with cresyl violet. The circular and circinate areas, corresponding to regions of demyelination, are outlined by dense accumulations of microglial phagocytes, which are much more numerous at the margins of the lesions. There are many small perivascular lesions. B, mid-brain, myelin stain. The perivascular character of the lesion is clearly shown. There is demyelination of the proximal portions of the third nerves (*a*). Myelin beyond the transitional between glia and Schwann cells is normal.

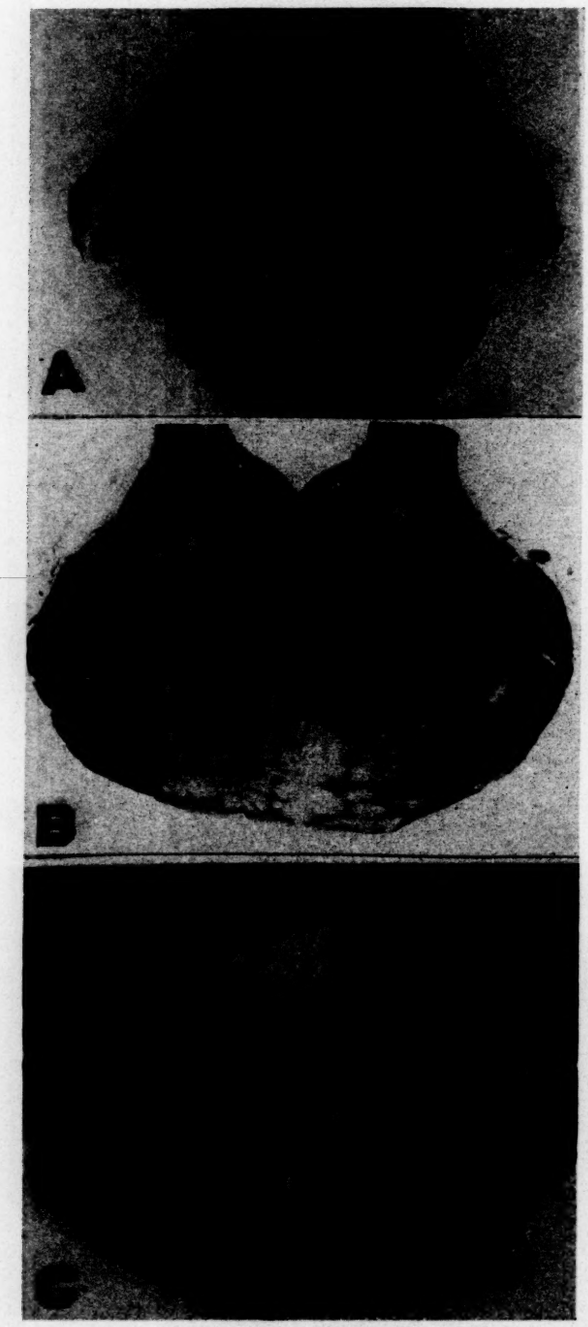


FIG. 6. Multiple sclerosis. A, section of pons from a case in which trigeminal neuralgia was a symptom; myelin stain. B, pons from a case of acute multiple sclerosis, showing a region of demyelination made up of numerous smaller lesions, often separated by a zone of incomplete demyelination. A large proportion of the smaller lesions are perivascular. C, pons from a case of multiple sclerosis; myelin stain. Midline lesion near the medial longitudinal fasciculi that had resulted in internuclear ophthalmoplegia.

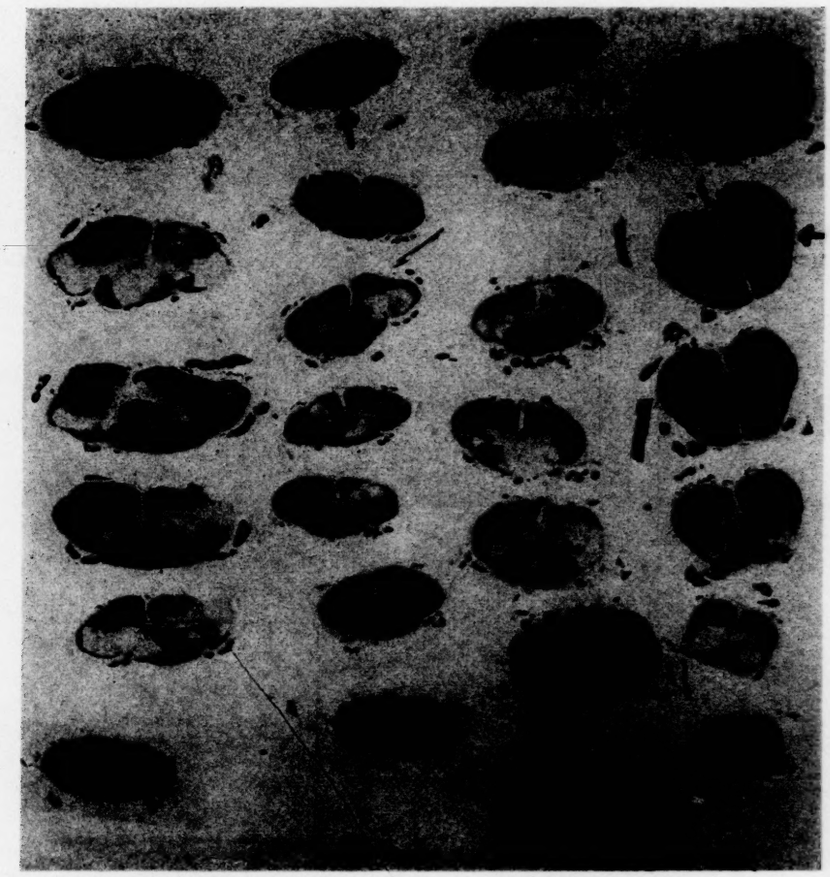


FIG. 7. Chronic multiple sclerosis; sections of each segment of the spinal cord from a long-standing case of multiple sclerosis, showing one or more lesions in a majority of the segments. Note some degree of secondary degeneration of the corticospinal tracts and, at the higher levels, of the medial fibers of the posterior columns (indicated by arrows).

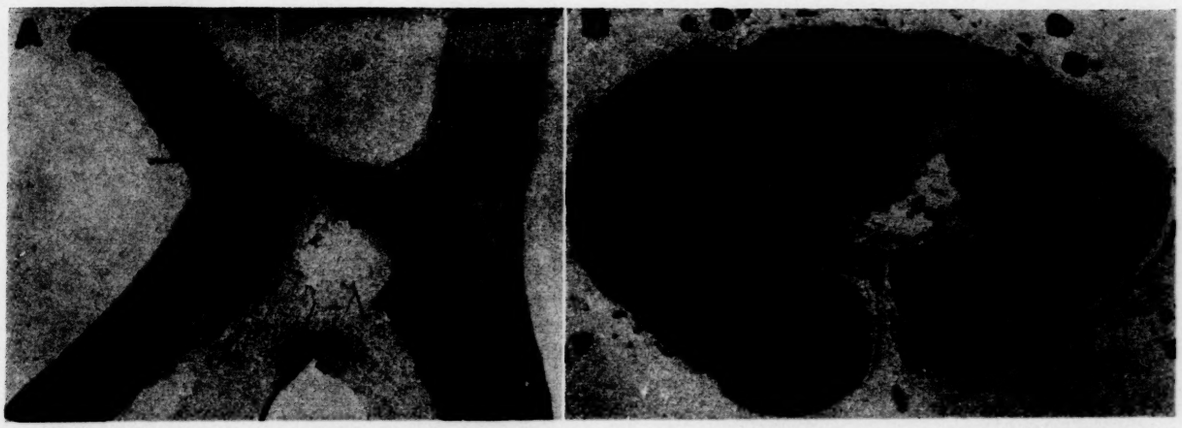
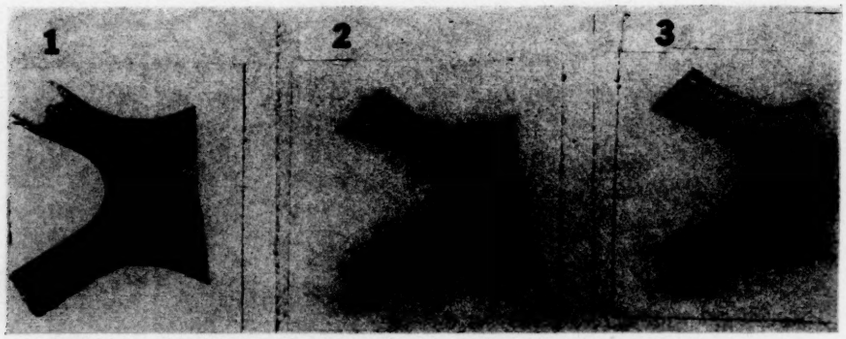


FIG. 8. Case 3. Multiple sclerosis. A, horizontal section of the optic nerves, chiasm and tracts. The myelin in the right optic nerve is destroyed and there is secondary degeneration of the uncrossed fibers in the right optic tract and of the crossed fibers in the left optic tract. B, myelin-stained section of the fifth thoracic spinal segment. The myelin in the anterior and lateral columns is degenerated and there is cavitation in the central gray matter and posterior column (*a*).



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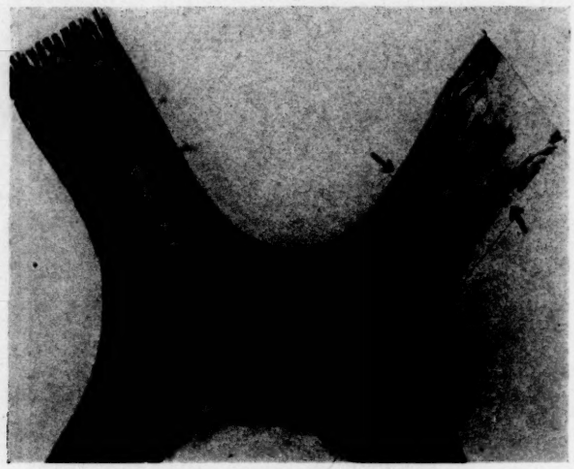

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FIG. 9. Multiple sclerosis. A, adjacent sections of a lesion of the optic nerve stained for myelin (1) fat (2) and fibrous glia (3) showing demyelination, a dense accumulation of microglial macrophages and gliosis. B, another level of the optic nerves of the same case. Note the numerous small perivenous lesions indicated by arrows.

secondary degeneration of the fiber tracts implicated by the lesions. In long-standing cases, however, with extensive involvement of the spinal cord and brain stem, a diffuse thinning out of the fibers in the corticospinal tracts, particularly in the lower segments of the cord, and of the posterior columns in the upper segments, representing secondary descending and ascending degeneration, indicates that eventually many fibers are destroyed. (Fig. 7.) This secondary degeneration is easily distinguished from the lesions because it is incomplete, corresponds to the site of fiber tracts and has the same configuration at many different levels. In some lesions there may be a great reduction in the number of axis cylinders (Fig. 15A), and some of the axis cylinders within the lesions exhibit degenerative changes. (Fig. 15A and B). An "axonal" reaction of nerve cells is rarely observed.

Coincident with the demyelination the oligodendrocytes degenerate and reactions of the microglia and astrocytes take place. There are, in nearly all of the more recent lesions, numerous rod-shaped and pleomorphic microglial cells, and large round macrophages. (Figs. 16 and 17B.) As in most degenerative processes this reaction is much more pronounced in the white than in the gray matter (Fig. 4A), and is often more intense at the periphery of the lesion, in the outer zone of demyelination and in a narrow surrounding strip where the myelin is only partly destroyed. An example of this is shown in Figures 5A and 13A where in a cresyl violet section the lesions are outlined by a prominent, deeply stained zone, representing large numbers of microglial phagocytes.

The reaction of the astrocytes consists of proliferation of both cells and fibers essentially no different from that commonly observed in other diseases. In and around some lesions, especially the early ones, there are plump

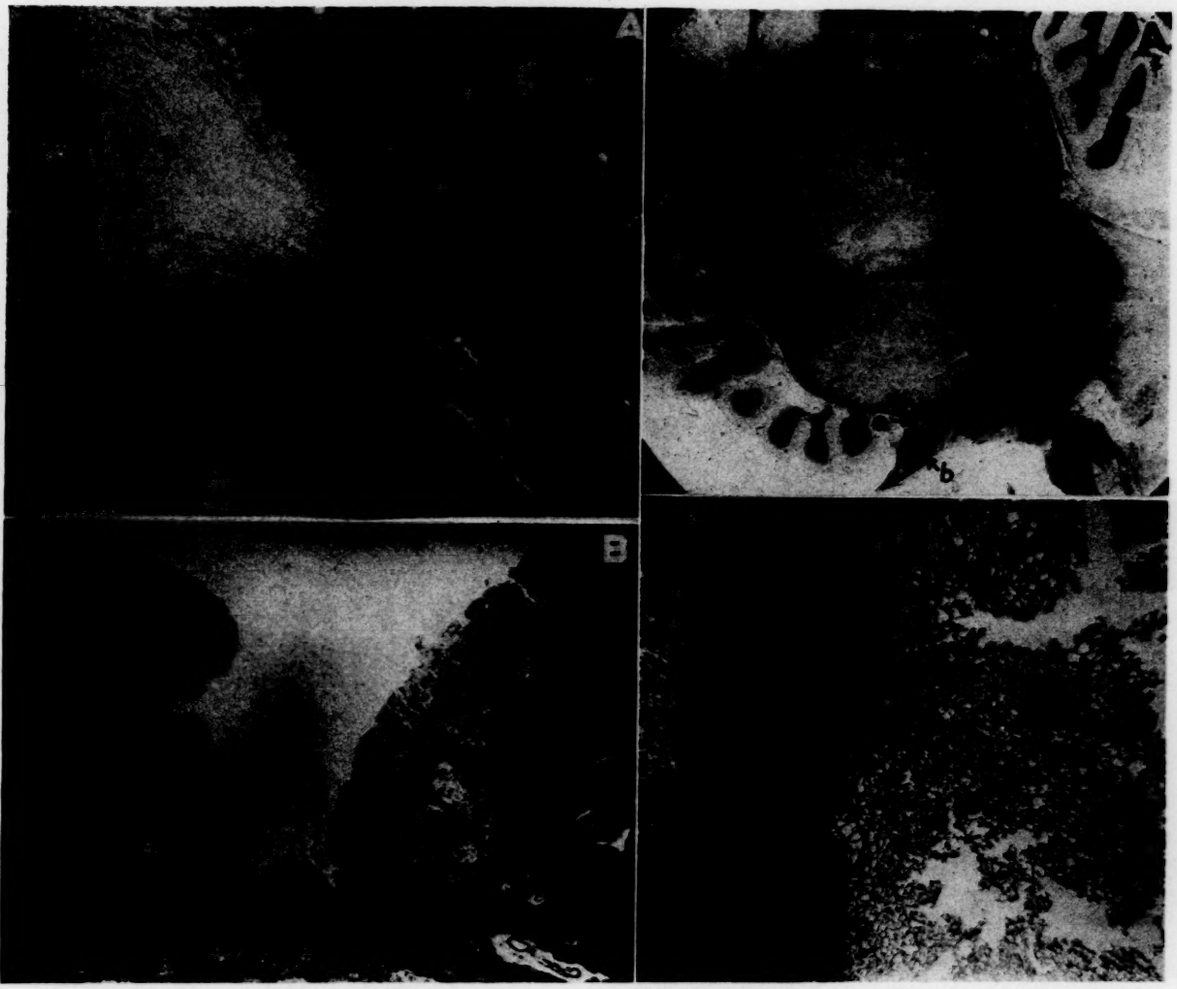

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FIG. 10. Chronic multiple sclerosis. A, myelin-stained section of the cerebral cortex and subcortical white matter. A shadow plaque is seen as an oval-shaped region in the right lower corner (*a*); here the myelin is pale but many fibers are preserved. In the upper left corner nearly all of the myelin has degenerated (*b*). B, acute multiple sclerosis (optic neuromyelitis) Case 4. Myelin-stained section of the anterior columns of a thoracic cord segment. The myelin has degenerated in multiple small foci, some of which are perivascular, on either side of the anterior fissure.

FIG. 11. Acute multiple sclerosis. A, myelin-stained section of the lateral part of pons and cerebellum. Several lesions of different size and age are seen and are separated by bands of partially degenerated myelin. There is a lesion involving the acoustic nerve at (*a*) which extends to but not beyond the transition zone (*b*). Lesion (*c*) is surrounded by a darker region of more recent demyelination. Note small perivascular foci at upper border of large lesion (*d*). The lower part of the small lesion to left of (*e*) is shown at higher magnification in Figure 12. B, myelin stain of the cerebral white matter. Two lesions are separated by a bridge of intact myelin. The lesion on the right has a reticulated appearance indicating partial necrosis of the tissue.

astrocytes with well defined cytoplasm and often with two or three nuclei. (Fig. 18B.) In older lesions there is a mat of fibrous glia which becomes exceedingly dense in the white matter and is less pronounced in the gray matter. In time the proliferation of microglia and astrocytes subsides, macrophages diminish in number, and the network of fibrous glia increases in density and becomes less cellular. (Fig. 18C.) At a later stage there is only a scattering of phagocytes, which eventually are found only in the perivascular spaces (Figs. 16A and 17B), and in very old lesions may finally disappear altogether as in Case 2.

Even in the oldest lesions nerve cells and a large proportion of the axis cylinders persist. All of the nerve cells in a completely demyelinated region may appear to be healthy al-

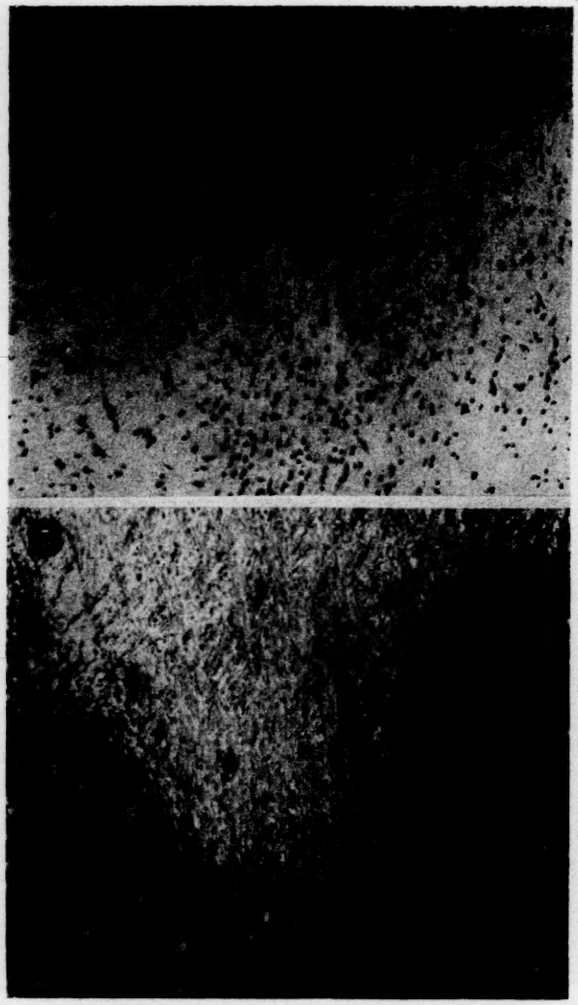

FIG. 12. Acute multiple sclerosis. Adjacent Nissl (*a*) and myelin (*b*) sections of the lower half of lesion (*e*) in Figure 11A. In A there is an increased number of pleomorphic and rod-shaped microglial cells corresponding to the area of early demyelination in B. The myelin sheaths are still visible and morphologically intact. Estimated age of lesion is two days.

though sometimes they are slightly diminished in number and show degenerative changes. (Fig. 17A.)

Individual lesions or regions of demyelination range in size from 1 mm. to several cm. in diameter and may involve the greater part of a cross section of the brain stem or spinal cord while lesions 4 to 6 cm. in diameter are sometimes present in the cerebrum. (Fig. 1.) Quite often a region of degeneration is made up of a number of smaller lesions which in chronic cases may be of widely different ages as indicated by the stage of microglial and astrocytic reaction. (Fig. 11A.) A conspicuous and interesting feature is demyelination around small and medium-sized veins. (Figs. 6B, 9 and 11A.) Large lesions may have a scalloped margin (Figs. 5 and 11A) which suggests that they result from the union of many small perivenous lesions. Some indication of a perivenous demyelination can be found in nearly every case but there are also large lesions in which no signs of it exist, although it is possible that even in these the initial degeneration may have been perivascular. The lesions sometimes form curious designs as in Figures 6B and 11A, again suggesting that a large region of demyelination is made up of smaller lesions. In some places there is actually a narrow strip between some of the adjoining smaller lesions in which the myelin is not completely destroyed. Some of the areas in one of these conglomerate lesions may have approximately the same appearance in a myelin

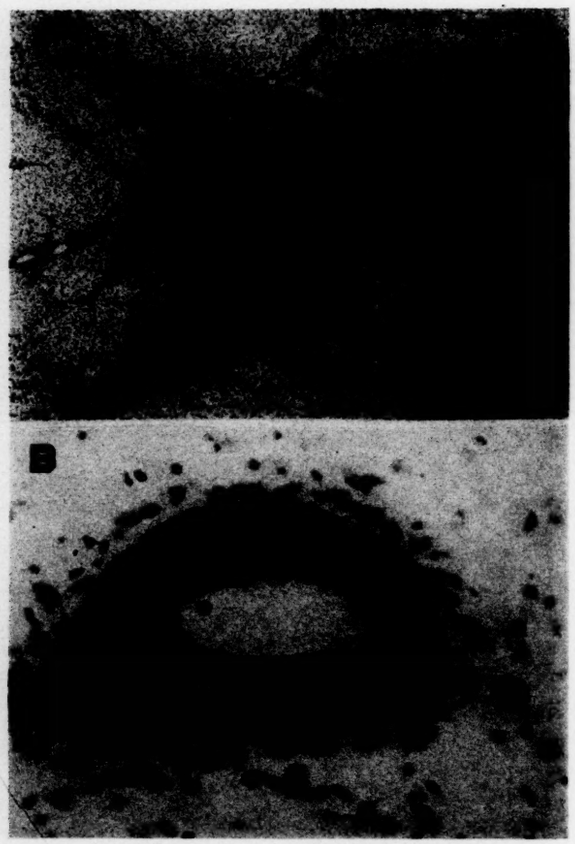

FIG. 13. Case 1. Acute multiple sclerosis. A, Nissl-stained section of one of the perivenous lesions in the pons showing perivascular infiltration and the microglial reaction corresponding to the region of demyelination. The microglial phagocytes are much more numerous at the periphery. B, same case; a perivascular infiltration with lymphocyets, plasma cells and histiocytes.

stain yet histologic study usually will show that they vary in age from one part to another and that the margin of a lesion may be more recent than its center, as if it had spread.

Necrosis of tissue is rare but occasionally there are lesions which have the general aspect of a softening. The ground matrix is loose and fenestrated (Figs. 11B and 18A), and there is necrosis of parenchymal elements as well as glial cell nuclei and even the small blood vessels. The end result is one or several adjoining cavities surrounded and traversed by a network of connective tissue (Fig. 8B) or, if the damage is less complete, a porous lesion with twisted skeins of fibrous glia throughout.

The disease does not show a decided preference for either gray nuclear masses or fiber tracts. It is more pronounced, as a rule, in the brain stem and spinal cord and there is usually some involvement of the cerebrum. The cerebellar hemispheres are seldom involved to any considerable degree. There are exceptional cases in which the spinal cord is not affected, at least so far as can be determined by sections taken at every segmental level (Cases 1 and 2), and others in which the disease is largely confined to the spinal cord with only slight involvement of the cerebrum or brain stem. The most common location of lesions within the cerebral hemispheres is in the white matter adjacent to the lateral ventricles, particularly outside the anterior and posterior horns. The central white matter is not often severely involved but may be, particularly in acute multiple sclerosis, and affection of the cerebral cortex is not usually extensive. In one of our cases, however, over thirty cortical lesions were demonstrated in one large section of the frontal lobes. (Fig. 3.) The pons and medulla nearly always contain lesions and like the spinal cord any part may be affected. Parts of the optic nerves are demyelinated in many of the cases but, since the orbital portions of the nerve were seldom examined in our cases, the preferential sites of the lesion cannot be stated. The optic chiasm is sometimes affected. Some of the lesions in the optic nerves and chiasm are small and have a perivascular distribution. (Fig. 9B.) The proximal parts of the spinal and cranial nerve roots are often involved but in our material the lesions never extended peripheral to the transition zone where oligodendroglia and astrocytes give way to Schwann cells and fibroblasts. (Figs. 11A and 5B.)

The histologic findings vary according to their age. It does not often happen that the age of a lesion can be determined with exactness. The earliest pathologic changes are rarely seen because death almost never occurs within a short time after the onset of the disease or if early lesions are present, as they may be even in a case of long-standing, determination of their age is difficult for it may be impossible to tell which lesion was responsible for any set of symptoms or findings. Cases of comparatively short duration are more useful and by applying knowledge derived from the study of dated infarcts and various other conditions, one is able to determine in a general way the features

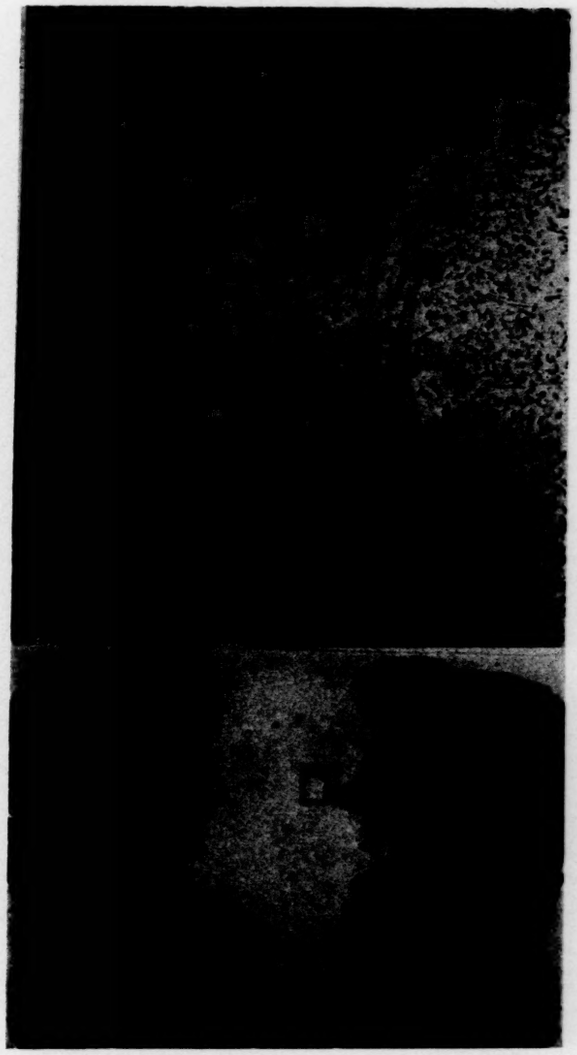

FIG. 14. Chronic multiple sclerosis. A, Cajal's silver stain showing integrity of most of the axis cylinders in the demyelinated hypoglossal nucleus and medial lemniscus. B, myelin stain of the lesion in the medulla. The part in A corresponds to the area outlined.

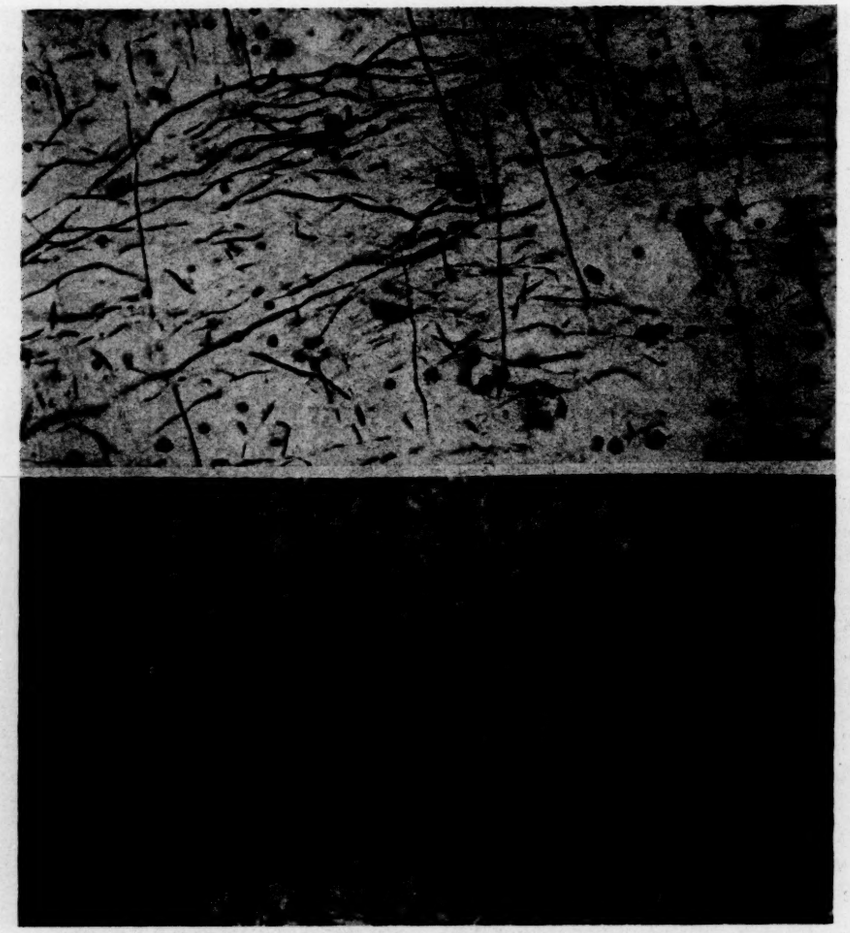

FIG. 15. Chronic multiple sclerosis. A, Cajal's silver stain of a chronic periventricular lesion in which most of the axis cylinders have disappeared and a few of the remaining ones show end-bulbs. B, same stain of another demyelinated focus in which the majority of the axis cylinders are preserved although abnormal.

which help to establish the age of a lesion within certain limits.

Figures 12A and B are photographs of an interesting lesion in a case of acute multiple sclerosis. In a section stained for myelin it measures 0.5 by 1.0 mm., has a sharply defined margin and is easily visible with the naked eye. Microscopic examination discloses myelin sheaths which are either faintly stained or unstained but morphologically intact. (Fig. 12B.) In adjacent Nissl and hematoxylin and eosin sections of the lesion glial cells are two or three times as numerous as in the surrounding tissues and consist chiefly of slender, fusiform microglial cells. (Fig. 12A.) There are many mitoses and many shrunken, deeply stained, pyknotic nuclei which are not present outside the lesion. Unstained or poorly stained, but still intact, myelinated fibers such as these are often observed in a recent infarct of twenty-four to forty-eight hours' duration. The microglial reaction therefore would be consistent with an age of forty-eight hours, more or less, and is in fact similar to that observed in carbon monoxide poisoning and infarction of approximately that age. The pyknotic nuclei are also like those found under similar conditions and probably represent degenerated oligodendrocytes. It would seem from these findings that the process which damages or destroys the myelin at the same time destroys oligodendrocytes and causes a microglial reaction. It is of interest that in this early lesion there was no perivascular infiltration although it was unusually pronounced in the other lesions. At a later stage the myelin sheaths undergo the customary degenerative changes; the microglia continue to proliferate, macrophages increase in number and size and

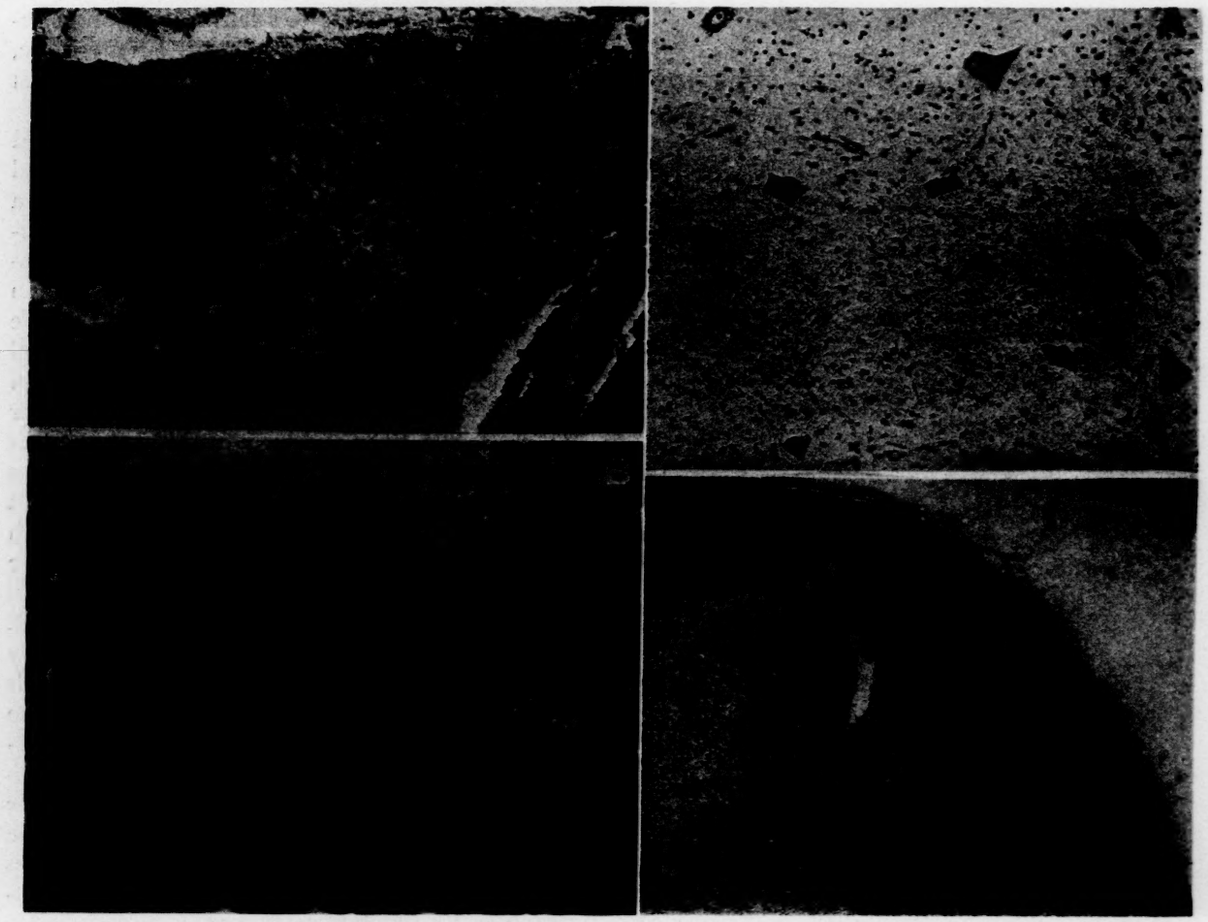

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FIG. 16. Case 4. Acute multiple sclerosis (Scharlach R stain for fat). A, demyelination of the anterior tract of a thoracic cord segment. Blood vessels are outlined by fatty macrophages in the perivascular spaces. B, Case 5. Subacute lesion in chronic multiple sclerosis (Sudan stain for fat). Demyelination in convolutional white matter and cerebral cortex. The large black bodies are macrophages filled with fat and the small round cells are a perivascular infiltration of lymphocytes and plasma cells.

FIG. 17. Chronic multiple sclerosis. A, Nissl stain; anterior horn cells in a lesion are preserved. Some are damaged more or less severely while others are quite normal. B, Case 5. Chronic multiple sclerosis. Sudan stain of medulla showing a region of demyelination composed of (*a*) an old lesion in which there is almost no fat and (*b*) a more recent lesion in which there are numerous macrophages filled with fat. The darker area (*c*) is normal myelin.

take up the products of degeneration. There is coincidental proliferation of astrocytes, indicated by an increased number and size of cells. Plump forms are observed during the earlier stages. Soon there is a progressive increase in fibrous glia. In time macrophages diminish in number and eventually are found only in the perivascular spaces (Figs. 16A and 17B) and in the oldest lesions there is little or no fat or indication of microglial activity, presumably because the products of degeneration have been removed. The reaction of the astrocytes also subsides, cells become less numerous, plump forms are no longer seen and only a dense, relatively acellular structure of fibrous glia is left. Even at this late stage nerve cells and a large proportion of the axis cylinders still persist. (Figs. 14A, 15B and 17B.)

There is generally perivascular infiltration in the earlier stages but, as already stated, it was not present in the earliest lesion seen in our material. It is often pronounced and perivascular cuffs several cells in thickness are not uncommon. (Figs. 13A and 16B.) Most of the infiltrating cells are lymphocytes but there are always some plasma cells and histiocytes. Neutrophilic leukocytes have not been observed. In some chronic cases perivascular infiltration is not present.

In summary, the pathologic changes which

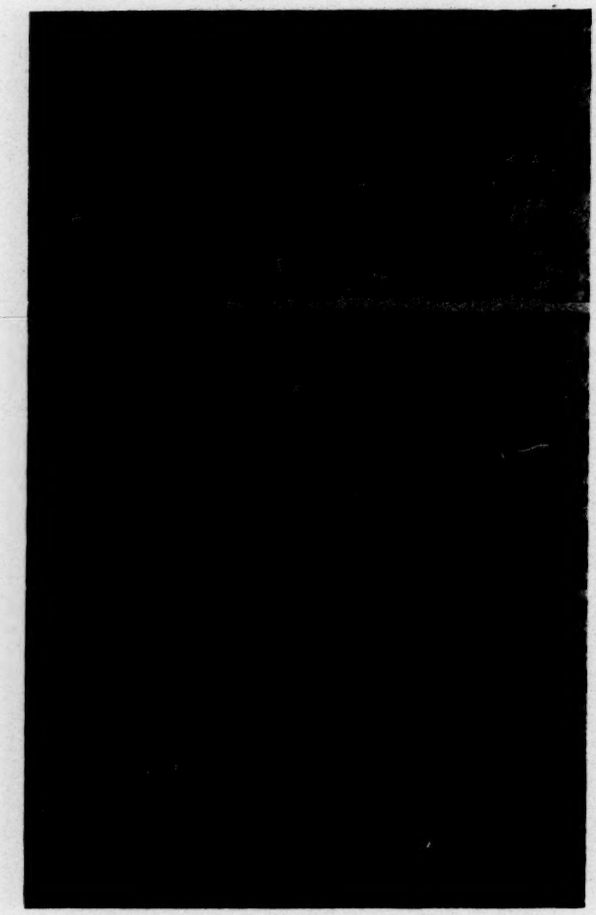

FIG. 18. Chronic multiple sclerosis. A, subacute lesion of reticulated appearance with numerous macrophages. B, plump astrocytes (*a*) and the smaller nuclei of microglial cells. C, the margin of an old lesion with only a few large astrocyte nuclei. Oligodendrocytes, the small dark nuclei on the left, are outside the lesion which lies to the right of the arrow.

characterize multiple sclerosis are: destruction of the myelin sheaths with relative sparing of axis cylinders, nerve cells and interstitial tissue; the multiplicity of lesions usually of different ages; their widespread, asymmetric distribution through the central nervous system; the relation of demyelination to veins; and the perivascular cuffs of lymphocytes and plasma cells.

RELATIONSHIP OF PATHOLOGIC FINDINGS TO CLINICAL PHENOMENA

In a condition characterized by multiple lesions occurring at different times it is not often possible to make an exact correlation between clinical manifestations and anatomic findings. Recent symptoms are likely to be obscured by residual earlier symptoms and it may be difficult or impossible to identify the lesion responsible for any set of symptoms. Furthermore, the inadequate clinical progress noted in most cases do not make the task easier.

Certain correlations are obvious and need only to be mentioned. It is clear that the clinical syndrome of retrobulbar neuritis is due to a lesion of the optic nerve. Diplopia in most instances is a symptom of internuclear ophthalmoplegia which is probably the most common ocular disorder in multiple sclerosis, and is due to involvement of the medial longitudinal fasciculus (Cogan et al.). Nystagmus is explained by implication of the vestibular pathways or nuclei in the brain stem. Unsteadiness, ataxia and incoordination are accounted for by lesions of the cerebellar peduncles within the brain stem. It may be added that in some cases with the most marked unsteadiness and ataxia there has been little or no disease of the cerebellum. Signs of disease of the corticospinal tracts, which sooner or later are a prominent feature in every case, may be caused by lesions at various levels in the spinal cord or brain stem or even in the cerebrum, and the same may be said of paresthesias and impairment of sensation. It is remarkable that there is comparatively little sensory loss, even in advanced stages of the diseases when the disorder of motor function is marked, and this may be true even after paraplegia in flexion has developed. The reason for this difference between motor and sensory manifestations is not clear since motor tracts are not any more likely to be involved than sensory tracts.

Certain other features of multiple sclerosis deserve comment. It is noteworthy that complete paralysis or loss of tendon reflexes is exceedingly rare and usually does not occur even after complete demyelination of a motor or reflex pathway. It must be concluded, therefore, that the demyelinated axis cylinders retain their ability to function more or less effectively. The presence in chronic cases of lesions which obviously are quite old clearly indicates that the myelin sheath does not regenerate. In considering the matter of remission of symptoms it may be pointed out that some degree of improvement is the rule with any acute or subacute pathologic condition of the central nervous system, as the disease process subsides. In multiple sclerosis it may be supposed that nerve cells and axis cylinders implicated in a lesion, although not destroyed, suffer temporary damage and de-

rangement of function but recover some degree of function after the acute phase is past.

B. ACUTE DISSEMINATED ENCEPHALOMYELITIS

(Post-infectious, post-exanthem, post-vaccinial encephalomyelitis, acute perivascular myelinoclasis)

Although many clinical writings of the eighteenth and nineteenth centuries refer to encephalitis and myelitis complicating measles, smallpox, chickenpox, vaccination against smallpox and rabies, the first satisfactory accounts of the pathology were provided by Bastiannse[4] in 1925 and by Turnbull and McIntosh[48] in 1926. Excellent papers by Perdrau,[41] Wohlwill,[53] Greenfield,[22,23] Van Bogaert[51] and Marsden and Hurst[35] followed within a few years and little of importance has been contributed to our knowledge of the pathology since that time. The subject has recently been reviewed by Finley.[19]

We have had the opportunity to study twelve cases most of which have been associated with measles, an upper respiratory infection or "influenza." Of these, the following six cases are described briefly in order to illustrate variations in the pathologic syndrome.

Illustrative Cases

Case 6 (MGH-9916A), a male, was twenty-two years of age. A measles rash appeared on January 7th and was followed two days later by fever, headache and stupor, and on the third day by stiff neck, coma and bilateral extensor plantar reflexes. Cerebrospinal fluid showed 1,280 cells per mm.^{3} and a protein of 334 mg. per cent. On January 11th grimacing and athetoid movements of the limbs were noted and there was retention of urine. Death occurred on January 12th. Postmortem examination revealed typical para-adventitial lesions in the medulla, pons and in cerebral cortex and white matter (Figs. 6 and 22), with only a few lesions in the spinal cord, cerebellum, mid-brain and optic thalamus. There was only slight degeneration of myelin in the para-adventitial regions. There was also a slight subarachnoid exudate. Diagnoses: post-measles encephalomyelitis and bronchopneumonia.

Case 7 (BCH-NP 48-45), a female, was twenty years of age. Measles rash appeared on April 11th and was followed two days later by temperature of 103°F., stupor, dilated and fixed pupils, stiffness of the neck and after that by deep coma, decerebrate rigidity and bilateral Babinski signs. Cerebrospinal fluid showed 1,360 cells per mm.^{3}, and a protein of 70 mg. per cent. Death occurred on April 20th. There were typical para-adventitial lesions, meningitis and perivascular infiltrates in diencephalon, mid-brain, pons and corpus callosum and relatively few lesions in the spinal cord, cerebellum and cerebrum. Diagnoses: post-measles encephalomyelitis and bronchopneumonia.

Case 8 (MGH-9540), a male, age eight years, was exposed to measles two weeks prior to acute onset of drowsiness, convulsions, stiff neck, trismus and bilateral Babinski signs. Cerebrospinal fluid contained 160 cells per mm.^{3} and protein of 156 per cent. Death occurred on the eighth day of illness. Typical para-adventitial zones of demyelination and microglial proliferation (Fig. 20), perivascular cuffing and meningitis were present. Maximal damage occurred in basal ganglia, cerebral white matter and cerebellum. There were no lesions in spinal cord. Diagnosis: probable post measles encephalitis.

Case 9 (BCH A49-515) a male, was forty-two years of age. Onset of illness with chills, fever, headache and hiccough occurred eight days prior to admission and was followed by temperature of 103°F., stiff neck, weakness of voice, dysphagia, restlessness, confusion and right facial weakness. Death occurred on the fourth hospital day. Pathologic findings were similar to those of the previous case, with the greatest number of lesions in medulla, pons, cerebellum and spinal cord. (Fig. 23A.) Diagnosis: postinfectious encephalomyelitis of unknown cause.

Case 10 (BCH-NP46-76), a male, age thirty-two years, because of a dog bite on November 18th, was given Pasteur treatment. Following the seventh injection on November 25th he complained of abdominal pain, urinary frequency and vomiting, and on the next day had flaccid paralysis of the legs and left arm, loss of tendon reflexes, urinary retention and mental confusion. Cerebrospinal fluid: cell count unknown, protein elevated. On December 5th dysphagia, dysarthria and nystagmus were noted. Coma developed and death occurred on December 8th. Para-adventitial zones of demyelination, meningitis and perivascular infiltration were most marked in the spinal cord, less in medulla and pons; few lesions were observed in the cerebellum, diencephalon and cerebrum. Diagnosis: post-vaccinial (rabies type) encephalomyelitis.

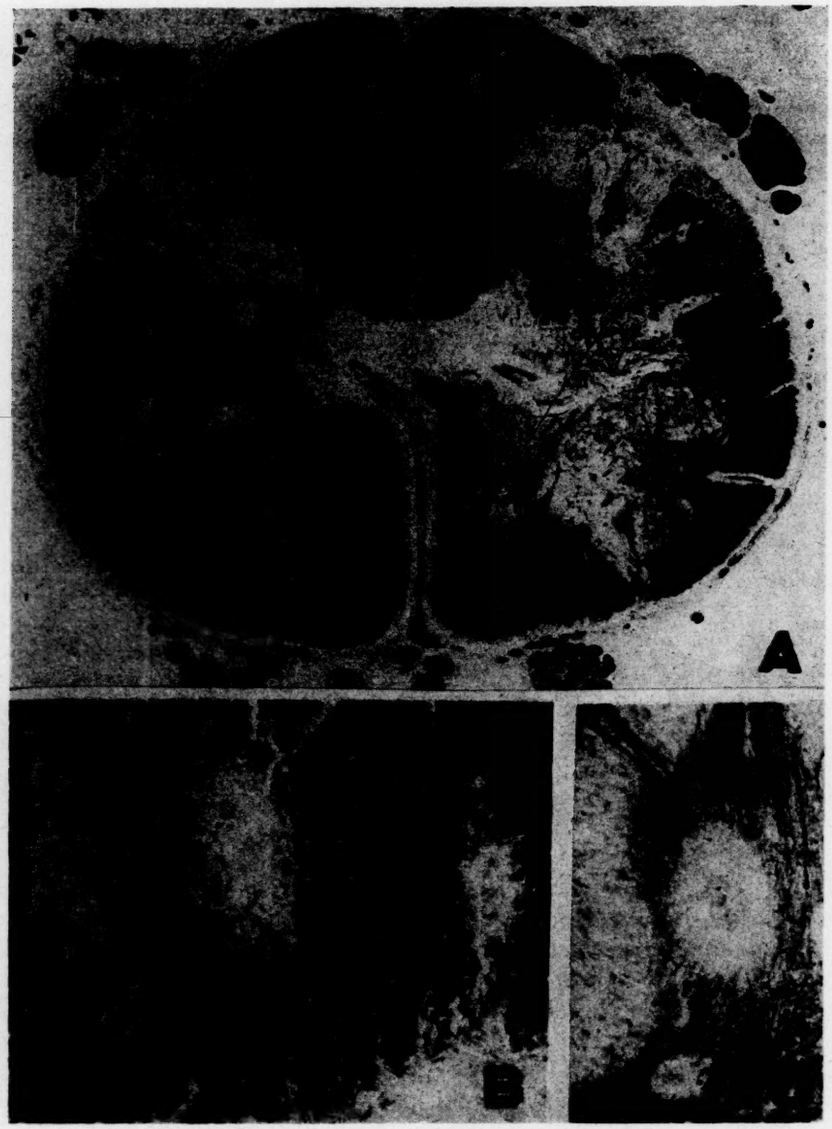

FIG. 19. Acute disseminated encephalomyelitis (Spielmeyer's stain for myelin). A, lumbar cord in a measles' case showing perivenous demyelination in both the gray and white matter. B, higher magnification of para-adventitial lesions in the anterior column of spinal cord and C, in the medulla in Case 6.

Case 11 (MGH-7826), a male, age twenty-four years, experienced rapid onset of weakness and numbness of legs on July 14th and urinary retention the next day. On July 17th motor and sensory paralysis had risen to the fifth thoracic segment. On July 20th the arms were weak and numb and three days later there was transient diplopia. The temperature was 102.8°F., cerebrospinal fluid: 934 white blood cells and 360 red blood cells per mm.^{3}, protein 134 mg. per cent. Difficulty in breathing, hoarseness and dysarthria followed. Death occurred on the thirteenth day of illness. The cervical cord was soft, diffluent, speckled with hemorrhages; meningitis, paraadventitial and subpial demyelination were present in the spinal cord, medulla and pons. (Fig. 21.) In the sections of the cervical cord small blood vessels were found to be necrotic. They were impregnated by fibrin and surrounded by fibrin and hemorrhages. (Fig. 25.) There were no lesions in the mid-brain, cerebellum, basal ganglia or cerebrum. Diagnosis: acute infectious encephalomyelitis, cause unknown with acute necrotic myelitis. This case is similar

to those reported by Hassin[28] and DeBuscher and Radermecker.[14]

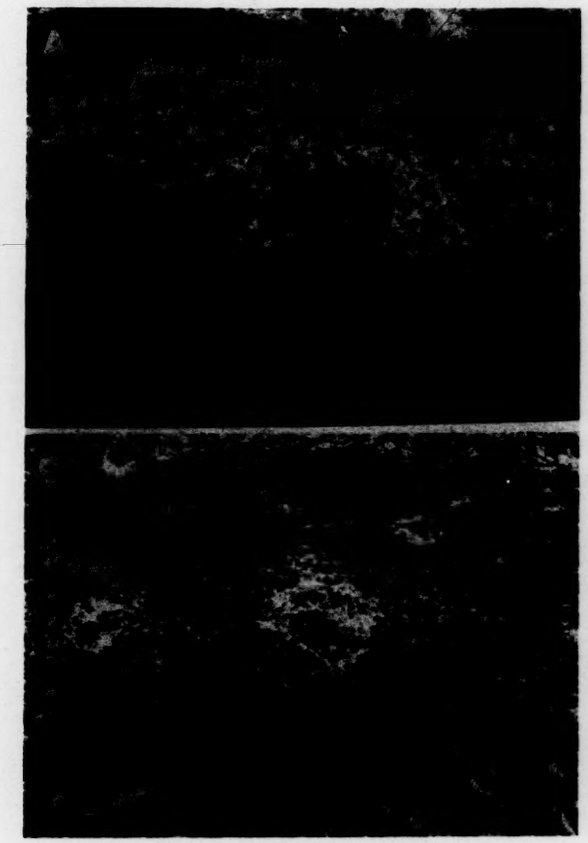

FIG. 20. Acute disseminated encephalomyelitis. A, para-adventitial focus of demyelination approximately 0.5 by 1.0 mm. in the medulla of Case 8. Around the vein in the center of the picture are many microglial cells the outlines of which are barely visible (Spielmeyer's stain). B, adjacent section of same lesion showing less severe degeneration of axis cylinders. The end-bulbs of damaged axons can be seen near the larger vessel. (Cajal's silver stain.)

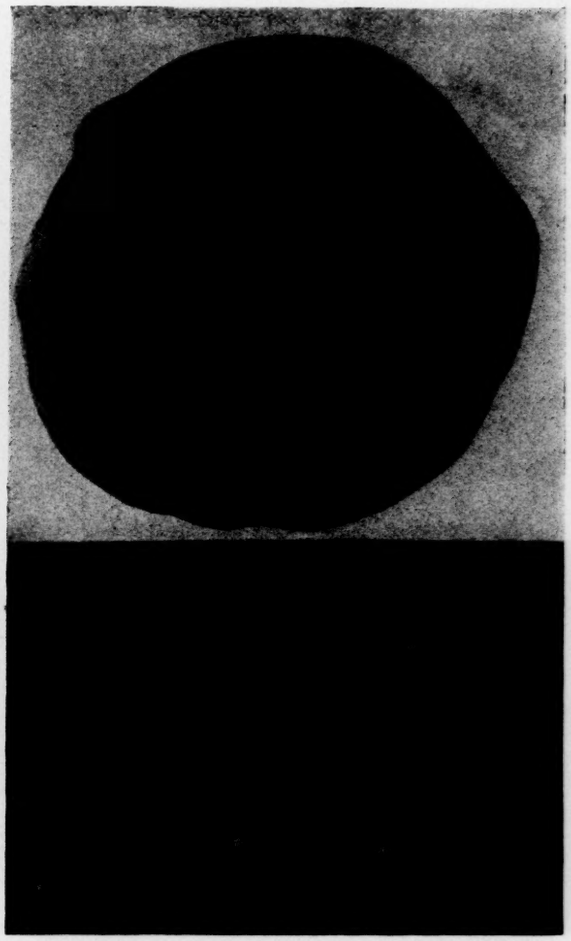

FIG. 21. Case II. Nissl stain; acute disseminated encephalomyelitis. A, thoracic segment of spinal cord. The congested blood vessels in both gray and white matter are outlined by large accumulations of para-adventitial microglial cells which appear as dark gray figures. B, perivenous and subpial microglial proliferation in the spinal cord.

Pathology of Acute Disseminated Encephalomyelitis

No distinctive abnormalities of the brain or spinal cord can be detected with the naked eye. Congestion of blood vessels in the spinal cord and the brain is commonly observed but may be due largely to terminal respiratory difficulty. In one of our post-measles cases there were several petechial hemorrhages scattered through the cerebral white matter and the middle cerebellar peduncles. In Case II the cervical cord segments were abnormally soft and slightly swollen.

Microscopic examination discloses innumerable lesions consisting of zones of perivenous (para-adventitial) demyelination which constitute the most important and distinguishing quality of the disease. They vary in size from 0.1 to 1.0 mm. in diameter and are found around veins of any size but chiefly small or medium-sized ones. (Fig. 19.) The myelinated fibers within the lesion usually have disappeared or at most only a few remain. There are cases (e.g., Case 6) in which there is almost no degeneration of myelin. By contrast Bielschowsky or Cajal silver stains demonstrate the integrity of the axis cylinders although tortuosity, thickening and end-bulbs indicate some damage (Fig. 20B) and in one case of measles all the axis cylinders were destroyed. Another striking feature is demyelination identical with that

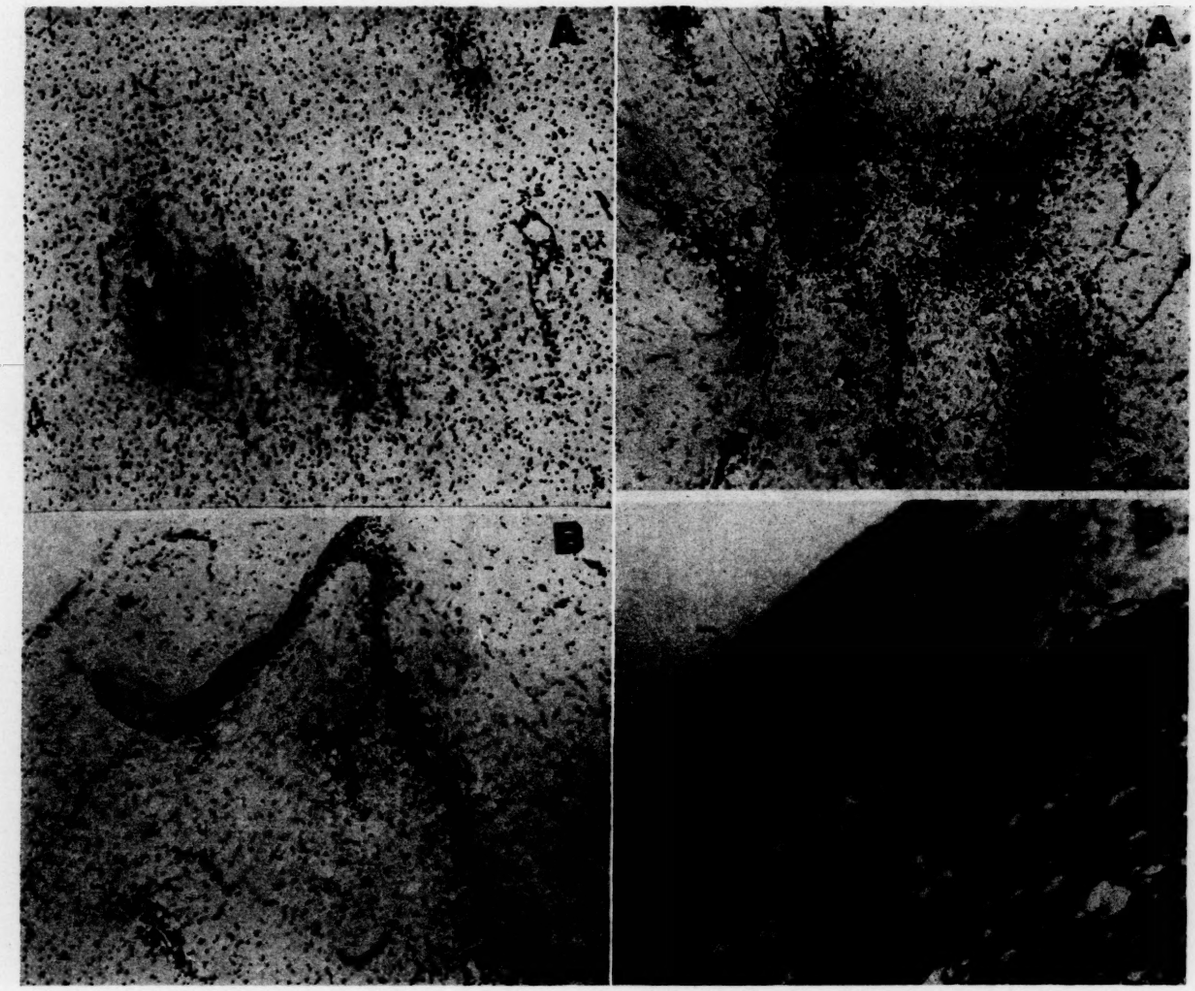

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FIG. 22. Case 6. Nissl stain; acute disseminated encephalomyelitis. Para-adventitial foci of proliferating microglial cells. In A the veins are seen in cross section and in B in longitudinal section.

FIG. 23. Acute disseminated encephalomyelitis. A, several lesions in anterior horn of a segment of cervical spinal cord. This shows the relation of lesions to vessels, the perivascular cuff of inflammatory cells, the para-adventitial microglial cells and the relative sparing of nerve cells. (Case 9, Nissl stain.) B, degeneration of myelinated fibers in subependymal region of the lateral ventricle. Note swollen myelinated fibers and several fatty macrophages. (Case 7, Loyez stain.)

observed in the para-adventitial lesions, in a narrow zone beneath the pia, in the spinal cord and brain stem, i.e., parts of the nervous system where fiber tracts lie next the pia (Fig. 21B), and rarely in the cerebral and cerebellar cortex. It is especially pronounced along the anterior sulcus of the spinal cord and in severe cases may involve the entire circumference of the spinal cord. Subependymal demyelination, as described by Wohlwill[53] (Fig. 23B), was observed in one case in the walls of the lateral and third ventricles.

In hematoxylin and eosin or Nissl sections there is a perivascular zone of increased cellularity, corresponding to the region of demyelination. (Figs. 21A, 22, 23A.) The reacting cells consist largely of pleomorphic microglia (Fig. 24A), often containing surprisingly little fat, but large, round macrophages are present in older lesions. The cellular reaction and the condition of myelin and axis cylinders are the same in the perivascular, subpial and subependymal lesions. Cells with pyknotic nuclei, probably degenerated oligodendrocytes, are regularly observed within the lesions. An occasional neutrophilic leukocyte or plasma cell may be found in the para-adventitial zone, i.e., outside the Virchow-Robin space. Nerve cells within the lesions are sometimes degenerated but, as a rule, are affected

FIG. 24. Case 6. Nissl stain; acute disseminated encephalomyelitis. A, irregularly shaped nuclei of proliferating microglial cells around a small vein in the cerebellum. B, infiltration of Virchow-Robin space of another small vein. The infiltrating cells are lymphocytes, histiocytes; a few neutrophilic leukocytes and plasma cells are also present. C, small artery with lymphocytes, plasma cells, histiocytes and neutrophilic leukocytes in the Virchow-Robin space.

relatively little. There may be a few plump astrocytes in the periphery of the demyelinated zones, but astrocytic proliferation is slight in the early stages.

There is cellular infiltration of the Virchow-Robin spaces of the veins which the lesions surround. In some cases there are only a few cells and in others enormous numbers. The degree of the perivascular infiltration is not proportional to the severity of the para-adventitial changes. The cells are lymphocytes, plasma cells, histiocytes (Figs. 24B and C) and cells which Turnbull and McIntosh[48] referred to as plasmacytoid

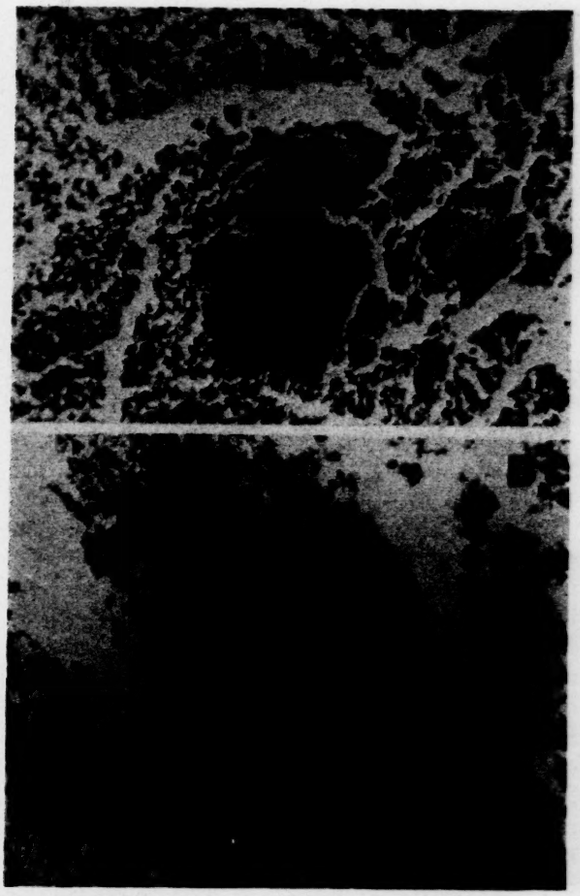

FIG. 25. Case 11. Acute disseminated encephalomyelitis. A, necrosis of tissue and small hemorrhages in cervical segment of spinal cord (hematoxylin-eosin stain). B, small vein in cervical cord showing damage and fibrin impregnation of vessel wall and perivascular exudate of fibrin.

elements. The latter are pear-shaped or oval with slightly basophilic cytoplasm and round nuclei containing several nodes of chromatin, but lacking a clock-face arrangement, and are probably large lymphocytes or young plasma cells. Lymphocytes always predominate but in some cases there is a high percentage of plasma cells.

There is usually only slight meningeal infiltration which tends to be spotty. The infiltrating cells are of the same type as those in the Virchow-Robin spaces. There may be changes in the cerebral cortex that do not appear to be related to blood vessels, consisting of an increase in microglia, in the form of diffusely scattered rod-shaped cells and of swollen astrocytes. A few nerve cells are destroyed in some of these lesions.

Vascular engorgement is a common finding. Infrequently there are a few small punctate hemorrhages, which are probably agonal as

there is no reaction of neutrophilic leukocytes or blood pigment. Necrosis of the small blood vessels, exudation of fibrin for some distance around the vessel, together with tissue necrosis and small hemorrhages as in acute necrotizing hemorrhagic encephalopathy were observed in several segments of the spinal cord in Case 11. (Fig. 25.)

The cerebrum, brain stem, cerebellum and spinal cord were affected in all the cases examined and so the disease was an encephalomyelitis in the strict sense. In the fatal cases the brain stem is always severely involved. There is in general a predominance of lesions in the white matter although the gray matter is by no means spared. In the cerebral cortex the disease was usually limited to the deeper layers. The lesions were numerous in both the tegmentum and base of the mid-brain, pons and medulla and in the spinal cord. In the cerebellum the central white matter and roof nuclei were chiefly involved. In one case of measles encephalomyelitis the lesions were most numerous in the diencephalon, internal capsules and mid-brain and in another in the brain stem and cerebellum. In the case which followed inoculation against rabies the most pronounced disease was in the spinal cord and medulla. No lesions were ever seen in the spinal or cranial nerve roots, spinal ganglia or peripheral nerves, though the latter were adequately examined in only one case. It is reasonable to suppose that the changes are less severe in the non-fatal cases.

In summary it may be said that this disease is characterized by perivenous, subpial and subependymal demyelinative lesions in the brain and spinal cord. Proliferation of microglial cells and adventitial histiocytes and cellular infiltration of the adventitial sheaths of blood vessels are the other important features.

This disease is easily distinguished from the neurotropic virus infections by the para-adventitial demyelination and cellular reaction and the lack of diffuse microglial proliferation and nerve cell destruction. There appear to be no important differences in the histologic findings whether the disease is associated with measles, chicken pox, smallpox, smallpox- or rabies vaccine innoculation. The agency which is responsible for these changes must be the same for all; their uniformity is a compelling argument against the virus of the antecedent disease being directly responsible. From both the clinical and pathologic evidence it is clear that this is an acute disease with a rapidy fatal or a brief, self-limited course. Recurrence rarely if ever takes place. Skin eruption is not a necessary antecedent since in Case 8, in which there had been exposure to measles, no rash ever appeared.

Relationship between Clinical Phenomena and Pathologic Findings

There is general agreement between the clinical manifestations and pathologic findings, i.e., the symptoms are those of a diffuse, widespread disorder of the brain and spinal cord, and of involvement of the meninges. There is an acute onset of confusion, somnolence and often convulsions, with headache and stiffness of the neck. Ataxia, myoclonic movements, athetosis or choreoathetosis may be observed. In the more severe cases stupor, coma and, at times, decerebrate rigidity may occur in rapid succession. With spinal cord involvement there is partial or complete paraplegia or quadriplegia, diminution or loss of tendon reflexes, sensory impairment and paralysis of bladder and bowel.

Patients may recover completely or be left with residual symptoms, which may be mild or severe. There may be only slight motor disturbances or pronounced spastic paraplegia and impairment of sphincter control. In children recovery from the acute stage is sometimes followed by a permanent disorder of behavior, mental retardation or epilepsy. As in most acute diseases of the central nervous system the functional derangement during the acute stage is out of all proportion to the permanent structural damage.

C. PROGRESSIVE CEREBRAL SCLEROSIS OF THE DEMYELINATIVE TYPE

Various forms of brain disease have been called cerebral sclerosis. During the early part of the twentieth century, as histologic technic improved, it became possible to distinguish between two major types, one a lipoid storage disease of nerve cells, e.g., Tay-Sachs amaurotic family idiocy, and the other a disease of the cerebral white matter for which the name centrolobar sclerosis seems most appropriate. Only the latter type is a demyelinative disease. Schilder[43] first called attention to it in 1912 and since that time more than 150 cases have been recorded. These cases are similar insofar as the white matter in the central parts of the cerebral hemispheres is predominantly affected in all but differ from one another with respect to the

age at which the disease begins, speed of evolution, length of clinical course and familial incidence. Subtypes based on these various clinical differences have been proposed. For example, familial cases which pursued a very chronic course from early life were described by Pelizaeus[40] and Merzbacher;[36] an acute familial variety beginning in the early months of life and progressing to death within one or two years was observed by Krabbe;[31] cases with the onset occurring later in childhood were recorded by Scholz;[44] and adult cases have been reported by Ferrara,[16] Van Bogaert and Bertrand,[50] and Van Bogaert and De Wulf.[52] The fallacy of basing a classification on age incidence and rate of progression is obvious.

Attempts to classify the cases according to variations in the morbid anatomy have been more successful but unfortunately overemphasis has at times been placed on some relatively unimportant detail of the pathology with the result that cases have been included which do not belong in this group. Einarson and Neel,[15] who have had a large experience with these diseases, have placed a great deal of stress on the glial cell changes and have actually included cases of diffuse glioblastoma. That there is no relation between cerebral sclerosis and neoplastic disease should be self-evident. Most authorities are agreed that there are at least two types of centrolobar sclerosis. Bielschowsky and Henneberg[5] from a study of two cases and a survey of the literature propose to divide them as follows: (1) The non-familial form that Schilder termed diffuse periaxial encephalitis which is characterized by demyelination involving a large part of the cerebral white matter, a conversion of the degenerative products of myelin into fat, and perivascular exudates of lymphocytes and plasma cells; (2) a familial form in which the degenerated myelin is converted into lipoid products of a kind not observed in other degenerative disease. The careful studies of Greenfield,[6,10,24] Einarsen and Neel[15] and Norman[38] have advanced our knowledge of the histopathology of both groups. Davison[12] has recently reviewed the subject.

Illustrative Cases

Case 12 (BCH-NP42-24), a male, was twelve years of age. At the age of seven years the patient began to complain of generalized weakness and was found to have Addison's disease. When nine to ten years old he became inattentive, forgetful and drowsy. He began to have convulsions and later developed right hemiplegia. Death occurred at the age of twelve years. There was total destruction of myelin including subcortical fibers, and almost equally severe loss of axis cylinders in the left frontal lobe, internal capsule, cerebral peduncle and pons, corpus callosum and on the right side in the medial part of the frontal lobe. (Fig. 26.) There was dense gliosis and, in the more recent lesions, large numbers of macrophages and perivascular infiltrates of lymphocytes. Anatomic diagnoses were Schilder's periaxial encephalitis and Addison's disease.

Comment. This presented certain unusual features such as the asymmetry of the demyelination, the involvement of frontal and sparing of the occipital lobes, and the affection of the subcortical fibers in several convolutions.

Case 13 (MGH 13340), a male, age ten years, suffered with progressive dementia and spastic paralysis of the legs beginning at the age of six years. An older brother had similar symptoms at about the same age. There was widespread symmetrical demyelination and degeneration of oligodendrocytes in the white matter of all parts of the cerebrum, the brain stem and cerebellum. In the degenerated regions there were granular bodies of metachromatic material and little or no neutral fat. The anatomic diagnosis was metachromatic leucoencephalopathy of the type reported by Greenfield[24] and others.

Case 14 (MGH-6968), a female, age twenty-five years, had progressive motor paralysis and sensory loss beginning in legs and rapidly ascending to trunk and arms. She later became blind, first in one eye and then in the other, and eventually developed convulsive seizures, aphasia and mental deterioration. The cerebrospinal fluid contained 70 cells per mm.^{3} and a protein of 85 mg. per cent. The course was steadily progressive. Death occurred six and one-half months after onset of illness. There were large foci of demyelination, measuring 3 to 4 cm. in diameter, in the left frontal and right occipital lobes, and similar smaller lesions in other parts of the cerebral white matter. There was necrosis of the lumbar and thoracic segments of the spinal cord and demyelination of both optic nerves. The anatomic diagnosis was subacute demyelinative leucoencephalopathy, probably acute multiple sclerosis.

Comment. Clinically, at least, before the onset of cerebral symptoms, the case might have been

regarded as an example of optic neuromyelitis. The postmortem findings consisted of a necrotizing process in the spinal cord, a degeneration of the white matter of the brain resembling that of Schilder's disease and multiple smaller lesions suggestive of acute multiple sclerosis.

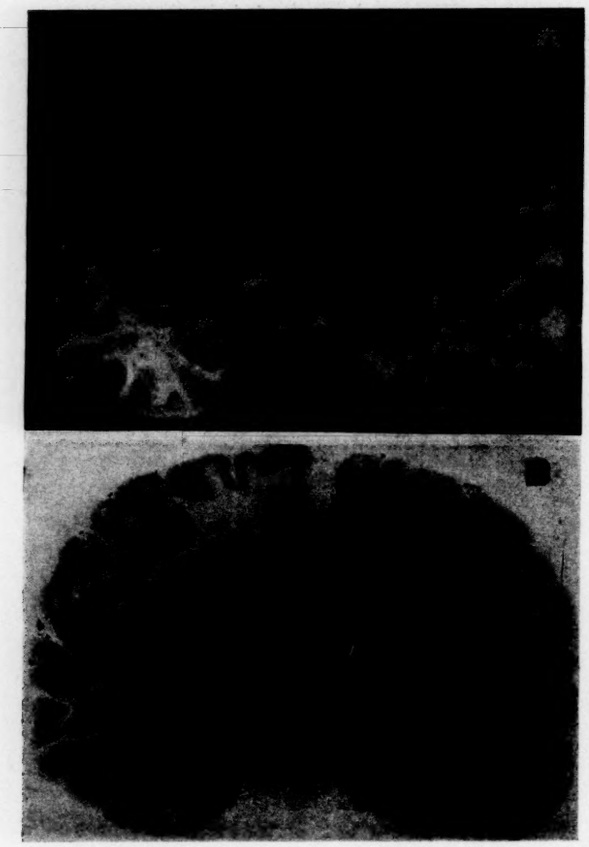

FIG. 26. Schilder's disease. A, coronal section of the fixed brain showing the grayish, translucent appearance of the degenerated white matter. (Case 12.) B, myelin section of the same block. Note degeneration of central and convolutional white matter including most of the subcortical fibers. (Loyez stain.)

Pathology of the Demyelinative Cerebral Scleroses

Schilder's Disease. Before the brain is sectioned nothing abnormal is seen except possibly a slight widening of the sulci and atrophy of the convolutions. In a few cases swelling of the brain, and rarely pressure cones, have been reported. Section of the cerebral hemispheres discloses a conspicuous alteration of the white matter. It is gray or brownish-gray, has a glistening, semi-translucent appearance, and is usually somewhat tough and rubbery and more firm than normal. There may be small cavities within the affected white matter. The degeneration, which is usually evident from macroscopic examination alone, involves the central and convolutional white matter. A narrow strip just beneath the cortical gray matter consisting largely of arcuate fibers is frequently, although not invariably, spared. In the majority of cases the disease is most advanced in the occipital lobes and appears to have spread anteriorly into the parietal and frontal lobes, although sometimes the oldest part of the lesion may be in the frontal lobes, as in Case 12. The corpus callosum is usually involved but not the anterior commissure. The process may extend into the internal capsule and cerebral peduncles and, as in Case 12, even into the base of pons, but more often it remains confined to the cerebrum. The basal ganglia are little if at all affected. In many cases the disease is not symmetrical in the two hemispheres. From histologic differences it can be said that all parts of the lesion are not of the same age. (Fig. 26.) The ventricles are slightly to moderately enlarged.

In myelin sheath stains there is as a rule one large area of demyelination, several cm. in width, in which there are no myelinated fibers, or at most only a very few. The margins of the lesions may or may not be sharply defined. In some of the cases reported as examples of Schilder's disease circumscribed foci from 0.1 to 2.0 cm. at a distance from the main lesion have been described; these may be confluent or separated by bands of intact myelin so as to form circinate and concentric patterns. In our opinion these are not cases of Schilder's disease but multiple sclerosis. The optic nerves and chiasm have been severely damaged in many of the published cases.

The axis cylinders are damaged almost to the same extent as the myelin sheaths. In the frontal lobes of Case 12 only a few axis cylinders remained. (Fig. 27B.) In the cortex nerve fibers are reduced in number, probably as a result of secondary degeneration.

The glial reaction varies. In most places, apparently the older parts, there is a loose network of fibrous glia with a small number of astrocytes. These cells have large and often paired nuclei and enormous processes. (Fig. 28.) Astrocytes with swollen, globoid or fragmented processes, apparently indicating a regressive change, are present in some places. Plump astrocytes are present in the early stages. In the older lesions there are relatively few microglial phagocytes, chiefly in the perivascular spaces, but in the more recent lesions macrophages

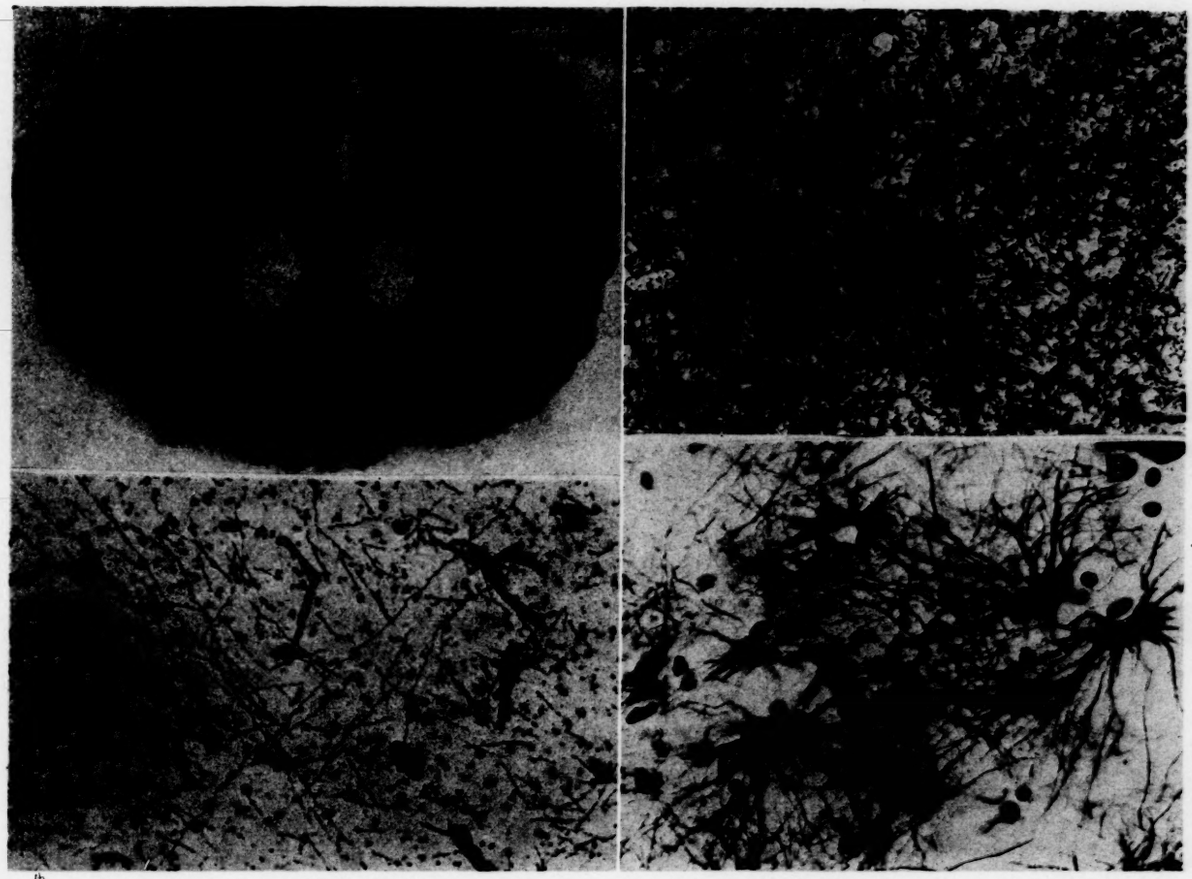

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FIG. 27. A, degeneration of the central and convolutional white matter of both frontal lobes in Case 13 of metachromatic leukoencephalopathy (Loyez myelin stain). B, loss of nearly all the axis cylinders in the central white matter (Case 12). The thin wavy lines are intact axis cylinders and the heavy black figures are thickened blood vessels (Gros-Bielschowsky method).

FIG. 28. Schilder's disease. A, gliosis of white matter in left frontal lobe (Case 12, Cajal's silver stain). B, higher magnification of same lesion to show giant astrocytes and fibroglia.

filled with fat are found in large numbers. The margins of the lesion, next the normal white matter, are sometimes outlined by macrophages as in acute multiple sclerosis. Most if not all of the oligodendrocytes seem to be destroyed. In the perivascular spaces enormous collections of lymphocytes and plasma cells are seen. The arteries and veins have thick walls with an abundance of reticulum in the adventitia, as in other chronic degenerative processes.

In the overlying cortex nerve cells may be reduced in number and some are shrunken and pale but the majority have a surprisingly normal appearance. There is comparatively little associated glial reaction. Secondary degeneration of the corticospinal tracts in the brain stem and spinal cord is always found.

In summary, the predominant pathologic change is massive degeneration of the central and convolutional white matter of the brain which appears to begin in one locus and to spread by contiguity. It differs from multiple sclerosis in the larger size of the lesion, the extent of axis cylinder degeneration which tends to parallel myelin destruction, and in the usual absence of separate lesions in the brain stem and spinal cord. Case 12 clearly indicates that symmetry of the cerebral lesions and involvement of the occipital lobes, which were stressed by Collier and Greenfield,[10] are not reliable criteria of this disease.

Case 14, of centrolobar sclerosis, had all the aspects of acute cerebral form of multiple sclerosis. The same can be said of the cases of Stauffenberg,[45] Haberfeld and Spieler,[26] Urechia, Mihalesau and Elekes[49] and Case 3 of Stewart,

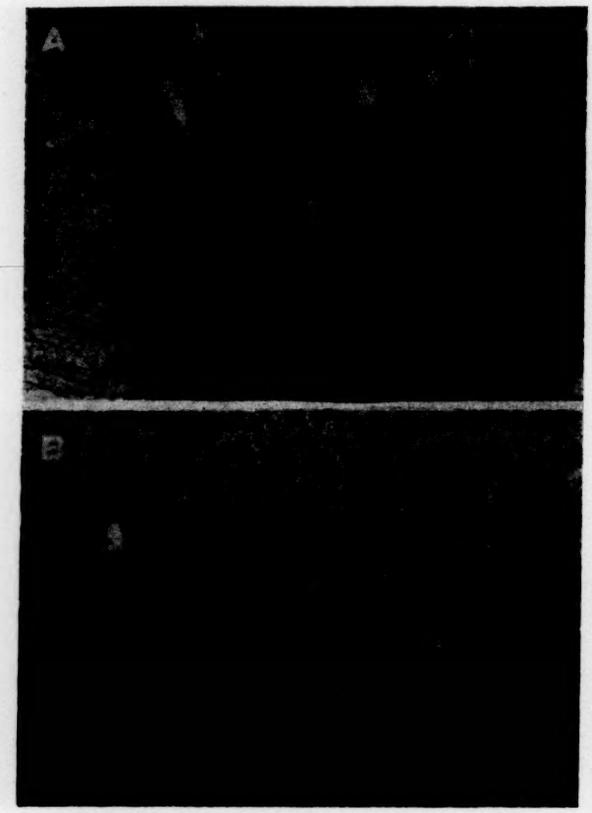

FIG. 29. Case 13. Spielmeyer's stain. A, cerebral cortex with radiating fibers on the left and subcortical white matter. There is relative sparing of the fibers just beneath the cortex. The round, black particles are the granular bodies, and they are most numerous at the margin of the demyelinated zone. B, higher magnification of a part of the same field to show details of the granular bodies.

Greenfield and Blandy.[46] The presence of disseminated lesions in the brain stem and spinal cord probably indicates that at least some of these are examples of acute multiple sclerosis with predominantly cerebral involvement. It should also be pointed out that the concentric and circinate patterns of myelin degeneration, referred to as concentric periaxial encephalitis by Balo,[3] is not distinctive and is actually a not infrequent finding in typical cases of multiple sclerosis. (Figs. 6B and 11A.)

Metachromatic Leucoencephalopathy. Here the degeneration involves the central and convolutional white matter of the cerebral hemispheres and the tissue has the same grayish or brownish-gray, translucent appearance. It is always symmetrical and there is a narrow subcortical zone in which the fibers are relatively spared. In advanced cases the greater part of the myelin in the cerebral hemispheres is destroyed. (Fig. 27A.) There are similar changes in the cerebellum and spinal cord (Brain and Greenfield[6]). The cerebral cortex, the subcortical fibers and basal ganglia are not directly involved. One of the most striking features of the disease is masses of granular material or "granular bodies." (Fig. 29.) Most of these bodies are large phagocytes but some, without a visible nucleus, cannot be identified as cells. Norman[38] pointed out that in frozen sections which have not passed through alcohol and xylol, thionine and toluidine blue will stain these granular bodies metachromatically, that is a pinkish-violet or green. In Case 13 some of the granular bodies were stained light brown by cresyl violet. In Scharlach stains they stain gray, or a gray-pink and not bright red as do macrophages filled with fat. The granular material, a degradation product of myelin, is stained by the Smith-Dietrich or Baker methods for phospholipids, the Schiff-Hotchkiss method for galactolipids and the mucicarmine stain. In several of the reported cases metachromatic material has also been demonstrated in the Kupffer cells, the cells of the collecting tubules of the kidney and in other organs, which it presumably reaches via the blood stream. In all parts of the white matter, even where the myelin is relatively intact, the oligodendroglial cells have either disappeared or their nuclei are pale and shrunken as if they are degenerating. Astrocytic gliosis occurs in the white matter but in our case was not nearly as striking as in the case of Schilder's disease. In the cerebral cortex there are usually no important changes in the nerve cells.

The principal pathologic features of the metachromatic leucoencephalopathy are: (1) massive destruction of the central white matter; (2) degeneration of the interfascicular oligodendrocytes, all through the white matter of the cerebrum and cerebellum; (3) granular bodies containing products of myelin in the form of phospholipids or galactolipids, but never cholesterol esters and fat; (4) the presence of this same material in the liver, kidneys and other organs.

It is not clear how many of the reported familial cases belong to this group of metachromatic leucoencephalopathy. It is probable that the cases of Bielschowsky and Henneberg,[5] Van Bogaert and Bertrand[50] and of Ferraro,[16] Greenfield,[24] Brain and Greenfield[6] and Norman,[38] and some of those of Einarsen and Neel[15] should be placed in this category. Krabbe[31] remarked that in his cases there was remarkably little material that stained with osmic acid and

it may be that they also belong to this group. In many of the older cases the pathologic material was not examined by technics which would have demonstrated the metachromatic bodies. It should be pointed out that Alzheimer, Nissl, Witte and Kaltenbach had all observed metachromatic substances in cases of cerebral sclerosis.

Relationship of Postmortem Findings to Clinical Phenomena

In centrolobar sclerosis the outstanding clinical finding is progressive deterioration of mental functions resulting eventually in dementia. Blindness, which is a common symptom, is usually related to the severe and often early involvement of the occipital lobes though the optic nerves may also be affected. Varying degrees of paralysis and other disturbances of motor function usually occur sooner or later and are explained by involvement of corticospinal tracts and other motor pathways. Deafness, which has been reported, would be accounted for by bilateral disease in the temporal lobes. In Schilder's disease the clinical findings like the lesions may be asymmetrical; there may be hemiplegia hemianesthesia or aphasia. Increased intracranial pressure accounts for the headache and papilledema in some of the reported cases.

In metachromatic leucoencephalopathy flaccid paralysis with loss of tendon reflexes, as reported by Brain and Greenfield,[6] correlates with their finding of metachromatic bodies and degeneration of oligodendroglia in the spinal cord. Familial incidence is also an important distinguishing feature.

The cases with large cerebral foci of acute demyelination differ from the above in the acute onset, rapid course, asymmetry of neurologic findings and manifestations of spinal cord and brain stem involvement. It seems likely for reasons already given that these are cases of multiple sclerosis.

D. ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOPATHY

(Affection Encéphalique Localisée of Gayet, Acute Primary Hemorrhagic Encephalitis of Bückler, Inferior Hemorrhagic Polioencephalitis of Oppenheim and Acute Hemorrhagic Leucoencephalitis of Hurst)

Many cases have been reported under these titles during the last seventy-five years but a survey shows that they have little in common other than a tendency for the lesions to be hemorrhagic. As a result of more careful pathologic study it is possible to distinguish several different groups. The superior hemorrhagic polioencephalitis of Wernicke is recognized as a distinct entity, known now to be due to vitamin B_1 deficiency. The brain purpura of Schmidt also has characteristic pathologic qualities which will be discussed later. Of the remainder the largest number are examples of acute necrotizing hemorrhagic encephalopathy and have been reported under the titles given in the heading of this chapter, by Leyden,[33] Gayet,[21] Bückler,[8] Brie,[7] Oppenhein,[39] Strumpell,[47] Levy[32] and da Fano,[11] Baker,[2] Hurst,[30] Henson and Russell[29] and Adams, Cammermeyer and Denny-Brown.[1] To date nine cases have been observed, at the Massachusetts General and Boston City Hospitals. The following case, previously reported, may be taken as a typical example of this disease.

Illustrative Case

Case No. NP46-68, B.C.H., a male, was forty-six years of age. Eight days following a period of malaise and lassitude there was an acute onset of headache, stiff neck, fever and drowsiness. The cerebrospinal fluid contained 3,365 cells per mm.^{3} of which 95 per cent were neutrophilic leukocytes, protein 226 mg. % and sugar of 51 mg. per cent. Coma and bilateral Babinski signs developed within a few hours, and death occurred forty hours after onset of neurologic symptoms. There was widespread hemorrhagic necrosis of the white matter in the right frontal and parietal lobes, corpus callosum and internal capsule, and to a lesser extent the left frontal lobe. (Fig. 30A.) The anatomic diagnoses were: acute necrotizing hemorrhagic encephalopathy and bronchopneumonia.

Pathology of Acute Necrotizing Hemorrhagic Encephalomyelopathy

Acute Necrotizing Hemorrhagic Encephalopathy. The brain lesion is characteristic and diagnosis can be made from inspection of the gross material. Section through the cerebrum or brain stem discloses a large asymmetrical focus, usually several centimeters in diameter where the tissue in the early stages is pink or grayish yellow, speckled with multiple small hemorrhages, swollen and soft, sometimes to the point of liquefaction. The margins of the lesion are not sharply defined. In the cerebrum only the central and convolutional white matter is af-

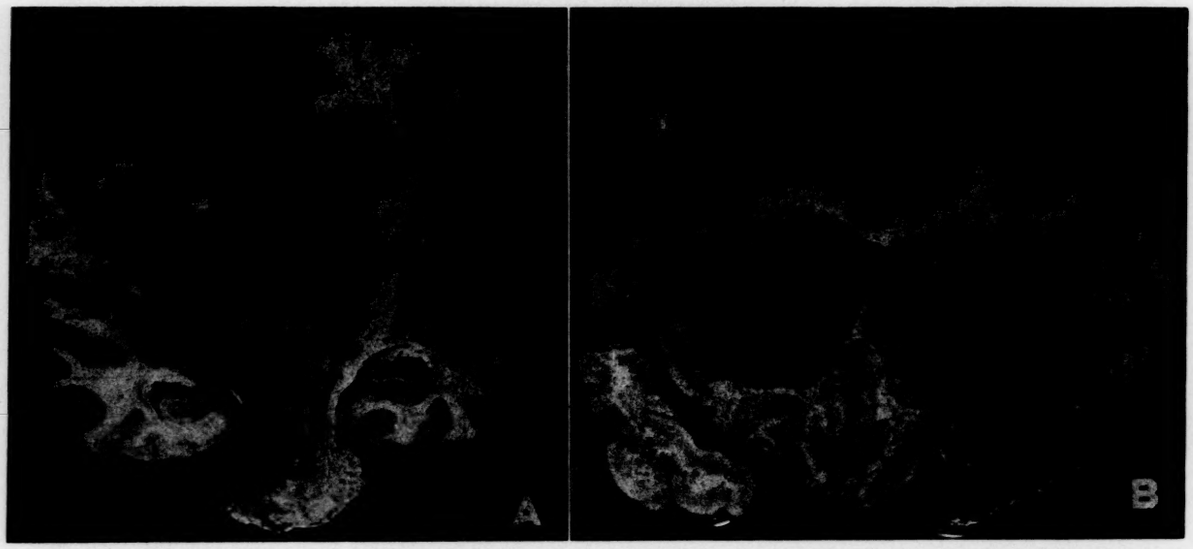

FIG. 30. Acute necrotizing hemorrhagic encephalopathy. A, coronal section showing hemorrhagic discoloration and softening in the central and convolutional white matter and corpus callosum (Case 15). Compare with Figure 2B of Schilder's disease. B, brain purpura. Punctate hemorrhages are present in the corpus callosum, white matter of both frontal lobes and internal capsules.

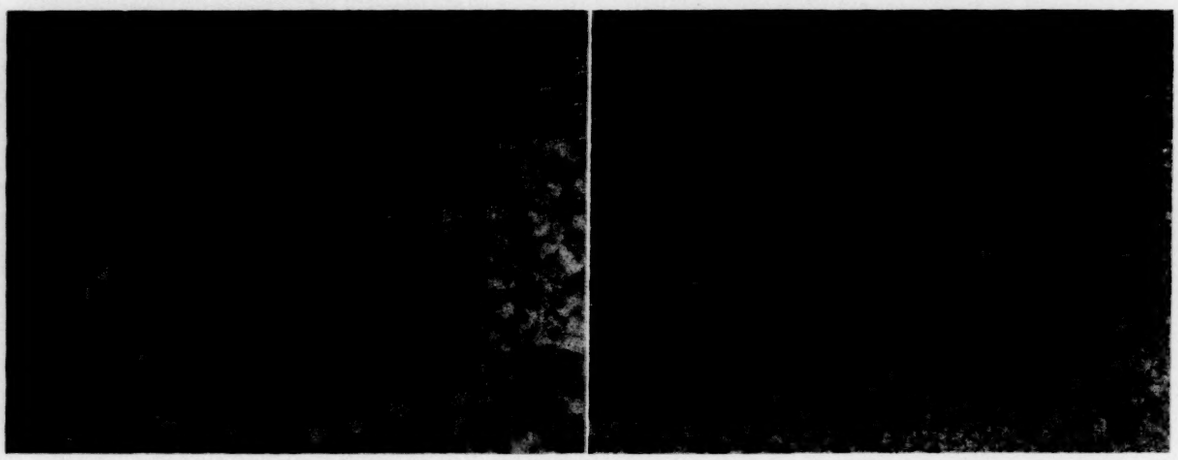

FIG. 31. Case 15. Hematoxylin-eosin stain. Acute necrotizing hemorrhagic encephalomyelopathy. A, small vessel encircled by fibrin and neutrophilic leukocytes. B, proliferating microglial cells in edematous perivenous zone.

fected in much the same manner as in Schilder's disease. In the brain stem the disease is more symmetrical, is usually located in the pons and mid-brain and involves both gray and white matter indiscriminately. Although the lesion is sometimes confined to the brain stem, it usually extends upward into the cerebral peduncles and internal capsules and posteriorly into the cerebellar peduncles.

The principal histologic changes are necrosis of small blood vessels, necrosis of brain tissue around those vessels with intense cellular reaction, multiple punctate hemorrhages and an intense inflammatory reaction in the Virchow-Robin spaces and meninges.

The vascular changes consist of varying degrees of necrosis, from complete destruction of all elements of the vessel wall to pyknosis and eosinophilia of some of the cells. Fibrin impregnation of the vessel wall is a prominent feature. (Fig. 32A.) The changes occur in the small veins although occasionally small arteries are affected. In the brain stem where the lesions extend to the meninges there may be necrotic changes in some of the pial vessels. Many of the vessels within the lesions particularly the larger arteries and veins and all of the blood vessels outside the lesions are normal. Thrombosis does not take place. There are large numbers of neutrophilic leukocytes and fibrin in the Virchow-Robin

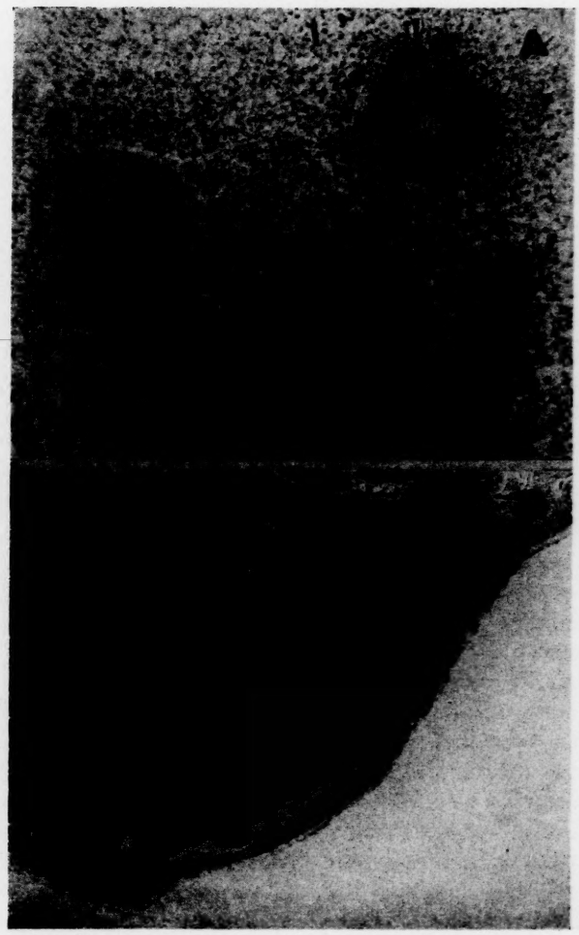

FIG. 32. Acute necrotizing hemorrhagic encephalomyelopathy. A, vascular and perivascular exudates of fibrin (*A*); perivascular tissue necrosis and leukocyte infiltration (*B*); and general tissue necrosis (*C*). Note that the stellate masses of fibrin end diffusely in the surrounding zone of leukocytic infiltration. (Case 15, Mallory phosphotungstic acid hematoxylin stain.) B, perivascular necrosis of myelinated fibers. The black dots are congested blood vessels and punctate hemorrhages. (Loyez stain.)

FIG. 33. Acute necrotizing hemorrhagic encephalomyelopathy. Perivascular necrosis of axones at different stages. A, degeneration and separation of axis cylinders around a dilated blood vessel with moderate perivascular infiltration. B, incomplete destruction of axis cylinders in the surrounding zone of leukocytic infiltration. Some of the degenerated axons are thickened and tortuous. C, complete destruction of axis cylinders; swollen argentophilic remnants are still visible. (Bodian silver stain.)

spaces and extending out into the para-adventitial tissues. (Fig. 31A.) Later on the infiltrating cells are largely lymphocytes and plasma cells. In all cases there are numerous punctate hemorrhages (Fig. 31B) confined to the foci of perivascular disease. There is severe destruction of brain tissue, most marked in the perivascular zone which roughly corresponds to the area of fibrinous and leukocytic infiltration. Here the myelin is completely destroyed (Fig. 31B) and the axis cylinders are damaged and often destroyed. (Fig. 33.) In an intermediate zone outside the perivascular lesion the tissue has a loose reticulated appearance and the myelinated fibers are pale and probably irreversibly damaged. Where gray matter is involved in the brain stem, the glia-cell nuclei and nerve cells are shrunken, darkly stained and pyknotic. In the most severe lesions there is necrosis of all the tissue in one large area of several centimeters. In less severe cases the tissue damage is limited more or less to the perivascular zones of the affected region. In the early stages glial cells show little reaction but later proliferation of microglia and eventually formation of macrophages (Fig. 31B) are observed and there are swollen astrocytes. The leptomeninges adjacent to the necrotic foci are also infiltrated

with neutrophilic leukocytes and later with lymphocytes and plasma cells.

As pointed out by Hurst,[30] these gross and microscopic changes constitute a distinctive neuropathologic syndrome. They differ from the sequence of changes in the neurotropic virus infections. Attempts to culture bacteria or isolate a virus from the brain in three of our cases were unsuccessful. The necrosis of tissue cannot be explained by the hemorrhage since there are lesions without hemorrhage and the hemorrhages are fresh even when the glial reaction is much older.

Another hemorrhagic condition, sometimes confused with acute necrotizing hemorrhagic encephalopathy, is brain purpura or pericapillary encephalorrhagia. In this the lesions are always small, 0.1 to 2.0 mm. in diameter and are confined to the white matter, particularly the corpus callosum, centrum ovale and middle cerebellar peduncles. (Fig. 29B.) Each lesion is situated around a small blood vessel, usually a capillary. The early lesion consists of a small, round, para-adventitial area in which both the myelin and axis cylinders are destroyed and which is usually though not always hemorrhagic. After a few days mononuclear cells containing droplets of fat surround the blood vessel. Vascular necrosis is rarely observed yet the vessels do not look perfectly normal. Fibrin exudation, perivascular and meningeal infiltrates of inflammatory cells and widespread necrosis of tissue are not observed, and in this respect brain purpura differs from acute necrotizing hemorrhagic encephalopathy. The etiology of brain purpura is quite obscure. In two of our cases it was associated with virus pneumonia. In another the onset occurred after an intravenous injection of arsphenamine. Four other cases were not associated with any disease.

Relationship between Pathologic Findings and Clinical Phenomena

In all of our cases of acute necrotizing hemorrhagic encephalopathy that have come to postmortem examination the disease was rapidly progressive and death usually occurred within two to four days and the longest period of survival was two weeks. The onset was almost apoplectic in some cases. Fever, headache, stiff neck and pleocytosis in the cerebrospinal fluid were observed in all the cases. Other major clinical manifestations have been drowsiness, stupor or coma, and convulsions. Hemiplegia was observed with unilateral lesions and quadriplegia and pseudobulbar paralysis with lesions of the brain stem. Patients with a similar clinical picture and thought to have the same disease have recovered with almost no residual symptoms.

Acute and Subacute Necrotic Myelitis or Myelopathy. Considerable uncertainty exists as to the pathology of conditions which on clinical grounds are diagnosed as acute or acute ascending myelitis. Judging from material which we have had the opportunity to examine it may be said that in many cases the morbid process is a demyelinative disease of one type or another, i.e., acute disseminated encephalomyelitis, acute multiple sclerosis or acute necrotic encephalomyelopathy.

The spinal cord disease in Cases 11 and 14 was of the acute necrotic or degenerative type. In one of these the lesions in other parts of the nervous system were typical of acute disseminated encephalomyelitis and in the other of acute multiple sclerosis. In Cases 3 and 4 it may be assumed that necrosis must have occurred because of the cavitation in the spinal cord. In another case recently examined, there had been an acute ascending motor and sensory paralysis with urinary retention and a pleocytosis in the cerebrospinal fluid of over 600 cells, mostly neutrophilic leukocytes. Death occurred in approximately two weeks. Postmortem examination disclosed an acute necrotic hemorrhagic myelopathy in the thoracic and cervical segments of the spinal cord. In still another case a similar clinical syndrome had been followed by optic neuritis and, three weeks later, by unilateral convulsions and by paralysis of the face and arm on one side. An acute necrotic hemorrhagic lesion was found in the cervical and upper thoracic segments of the spinal cord and a more recent lesion of similar type was present in the cortex and white matter of one cerebral hemisphere. A demyelinative lesion was present in the optic nerve.

It may be questioned whether myelitis is ever a separate disease. Certainly the pathologic changes in the cases which have been described are no different from those of the other demyelinative diseases which have already been considered. The same may be said of the clinical syndrome of "optic neuromyelitis." Some cases are obviously acute multiple sclerosis and others

including a majority of those which have been examined postmortem, an acute necrotizing disease.

Relationship of Pathologic Findings to Clinical Phenomena

Acute myelitis, whether demyelinative or necrotic in type, affects gray and white matter indiscriminately and the clinical manifestations therefore are those of involvement of motor and sensory tracts and anterior horn cells, viz., motor and sensory paralysis below the level of the lesion and paralysis of the bladder. As with any acute disease of spinal tracts there may be in the beginning abolition of all reflex activity so that the disease must be distinguished from conditions which affect the spinal motor neurones. The ascending course of the neurologic symptoms probably indicates that the disease begins in the lower parts of the spinal cord, later extends upward and may eventually involve the medulla. Meningeal symptoms may be present and correlate with the inflammatory reaction in the meninges. Some clinical improvement usually takes place in patients who survive. The residual damage is much greater in the necrotic than demyelinative forms. With relapse and the development of further spinal symptoms, the clinical syndrome suggests that the disease is multiple sclerosis or the condition reported by Foix and Alajouanine,[20] Greenfield and Turner[25] and others as subacute necrotic myelopathy.

OBSERVATIONS

Distinguishing Characteristics of the Different Demyelinative Diseases. No doubt every neuropathologist has had the impression that if he were but possessed of sufficient wisdom to interpret and analyze what he saw he could not fail to obtain a clue as to the cause and pathogenesis of these diseases. From the foregoing account of the pathologic changes it is evident that, aside from obvious clinical differences which are outside the scope of this discussion, each of the diseases discussed is characterized by distinctive anatomic features. These may be summarized as follows:

In *multiple sclerosis* it is the rule for the disease to be extensive with involvement of the spinal cord, brain stem, cerebrum and often the optic nerves and cerebellum. In some cases the spinal cord is affected almost exclusively and rarely, at least in the early stages, the disease is limited to the cerebrum and brain stem (Cases 1 and 2). Judging from clinical manifestations it may appear in the optic nerve many years before any other part of the nervous system is affected. The lesions are always multiple, usually sharply defined, and vary from 1 mm. to 4 cm. or more in diameter. They tend to be perivenous, or it may be stated that some perivenous lesions are nearly always present. (Figs. 5, 6, 9 and 11A.) In the cerebrum, apart from other lesions, extensive involvement adjacent to the lateral ventricles is a nearly constant finding. The lesions vary in appearance because of a difference in age. Except in cases of long-standing there is little degeneration of axis cylinders. The disparity between destruction of myelin and axis cylinders is far more pronounced than in any of the other demyelinative diseases. Degeneration of nerve cells and tissue necrosis are rare. The recent changes in chronic cases are identical with those of acute multiple sclerosis. In both there is conspicuous perivascular infiltration with lymphocytes, plasma cells and histiocytes. Meningeal infiltration is usually insignificant even in the acute states.

In *acute disseminated encephalomyelitis* the gross findings are not remarkable or distinctive. Small perivenous foci of demyelination from 0.1 mm. to 1 mm. or more in diameter are the prominent feature of the disease. This is usually accompanied by subpial demyelination in the spinal cord and brain stem and sometimes by subependymal degeneration. The lesions are widely distributed in most instances through the spinal cord, brain stem, cerebrum, cerebellum and at times the optic nerves. In some cases with the clinical features of acute myelitis, the lesions are predominantly or perhaps exclusively in the spinal cord. The brain stem or cerebrum are nearly always affected severely in the fatal cases. In the perivenous foci of demyelination axis cylinders may also be destroyed and nerve cells may be damaged. There are infiltrations of the Virchow-Robin spaces and the pia-arachnoid by lymphocytes, plasma cells, histiocytes and rare neutrophilic leukocytes. The lesions are all of approximately the same age and, in the material thus far examined, are comparatively recent with a microglial reaction consisting largely of pleomorphic cells, large macrophages and an early, slight reaction of the astrocytes. Degenerative changes in the blood vessels are rare.

In *Schilder's disease* there is massive degenera-

tion of large portions of the central and convolutional white matter of the cerebral hemispheres. A large proportion, and often all of the axis cylinders in the affected regions are destroyed. The degeneration is considerably more severe than is ever observed in multiple sclerosis. Intense secondary astrocytic proliferation, resulting in dense fibrous gliosis is an invariable finding. There is a microglial reaction consisting of cellular proliferation and the formation of macrophages which take up the products of the degeneration and stain red with scarlet R. Subpial degeneration is not observed and subependymal involvement is not a prominent feature, except where the large foci of degeneration extend up to the ependyma. Perivascular infiltration with lymphocytes, plasma cells and histiocytes is regularly observed. Proliferation of adventitial connective tissue is more pronounced than in any of the other demyelinative diseases. The statement has sometimes been made that the lesions of Schilder's disease are not sharply defined, as they are in multiple sclerosis, but we have not observed any such distinguishing characteristic. Lesions with sharply defined and with indistinct margins have been found in both diseases.

In *metachromatic leucoencephalopathy* the gross anatomic findings, consisting of degeneration of the central and convolutional white matter of the cerebral hemispheres, are similar to those of Schilder's disease. The most characteristic feature, and the basis for classification, are the granular bodies, which stain metachromatically with thionine, in the areas of myelin degeneration. At the same time there is an absence of neutral fat and cholesterol esters which are ordinarily products of myelin degeneration. As in Schilder's disease destruction of axis cylinders is severe, often approximating that of the myelin, and secondary degeneration of the corticospinal tract is a constant finding. The disease involves nearly all of the cerebral white matter, and at times the cerebellar white matter, optic nerves and the spinal cord. Brain and Greenfield[6] remarked that this disease affects fiber tracts which are not myelinated at birth or within the first three months of life. Degeneration of the oligodendroglia, not only in diseased regions but also where the myelin has not yet been affected, has been pointed out by Greenfield[24] who suggests that this is the primary change, and responsible for the myelin degeneration. A unique feature, unlike anything of a similar nature in any other disease of the nervous system, is the presence of the metachromatic material in the Kupffer cells of the liver and collection tubules of the kidneys.

Except for the superficial resemblance to Schilder's disease metachromatic leucoencephalopathy seems to have little in common with the other demyelinative diseases.

In *necrotizing hemorrhagic encephalopathy* the gross findings, which are characteristic, consist of large foci in the cerebral white matter and brain stem of soft, pinkish gray, yellowish tissue, dotted with numerous punctate hemorrhages so that it has an over-all hemorrhagic appearance. The involvement is focal, resembling Schilder's disease in its gross anatomic relations. Microscopic examination reveals fibrinous necrosis of the walls of small blood vessels, chiefly venules, surrounding which there are exudates of fibrin and inflammatory cells and a ring-shaped hemorrhagic zone. Demyelination, with moderate to severe destruction of axis cylinders, and appropriate secondary microglial and astrocytic reaction are found in these perivascular zones. The cells infiltrating the perivascular spaces are largely neutrophile leukocytes in the earliest stages and lymphocytes and plasma cells in the older lesions. There is similar infiltration of the subarachnoid space adjacent to lesions. That the hemorrhage is incidental and not responsible for the degeneration is indicated by the presence of perivascular degeneration and reaction without associated hemorrhage. It is moreover common to find fresh hemorrhage in the midst of an older microglial reaction. Because of the unusual features of vascular necrosis and the hemorrhagic character of the lesions the advisability of including this condition with the demyelinative disease might be questioned; but in view of other fundamental characteristics, the classification seems appropriate.

In *brain purpura* small capillary hemorrhages in the cerebral white matter are the most conspicuous feature of the morbid anatomy. However, as in acute necrotizing hemorrhagic encephalopathy, there may also be perivenous demyelination or more severe degeneration, and microglial reaction, not associated with any hemorrhage. Unlike necrotizing hemorrhagic encephalopathy there is no obvious disease of blood vessels, perivascular infiltration or meningitis of any consequence. The involvement varies in extent and degree from scattered,

small perivascular lesions to widespread, hemorrhagic degeneration.

Because of the perivenous nature of the lesions, their concentration in the white matter and the demyelinative characteristics there is some similarity between this condition and acute disseminated encephalomyelitis. The differences, however, are very striking and for the time being it probably should not be included in the group of demyelinative diseases.

A Comparison of the Pathology of the Demyelinative Diseases. Although the anatomic differences between the demyelinative diseases are quite unmistakable in most cases, there are at the same time striking similarities. In Table 1 an attempt is made to compare the principal pathologic changes of each disease. There is an obvious difficulty in making such a comparison because in some of the diseases death occurs in the early stages while in others it takes place much later. Thus the late effects of acute disseminated encephalomyelitis and acute necrotizing hemorrhagic encephalopathy have not been observed while the findings in the earliest stages of multiple sclerosis and Schilder's disease are rarely seen. Acute and chronic multiple sclerosis, acute disseminated encephalomyelitis, Schilder's disease and acute necrotic hemorrhagic encephalopathy have many features in common whereas metachromatic leucoencephalopathy and brain purpura differ to such a degree that it is doubtful whether they should be included in the same group.

When compared as to the disparity between degeneration of myelin and axis cylinders, it will be noted that this is most evident in multiple sclerosis and least in Schilder's disease. The form and distribution of the demyelination is in some respects similar in all. In all cases of acute multiple sclerosis and in the majority of the chronic cases there are perivenous foci of demyelination, indistinguishable from those of acute disseminated encephalomyelitis. Occasionally some large lesions in multiple sclerosis are obviously formed by a confluence of small perivenous lesions, and this may also occur in acute disseminated encephalomyelitis. In acute necrotizing hemorrhagic encephalopathy the perivenous distribution of lesions is almost as characteristic as in acute disseminated encephalomyelitis. In Schilder's disease, on the other hand, perivenous foci are rarely seen. The gross anatomic distribution of lesions in the cerebral form of acute necrotizing hemorrhagic encephalopathy is the same as in Schilder's disease. (Figs. 26 and 29.)

Subpial demyelination is most characteristic of acute disseminated encephalomyelitis, but also occurs in acute necrotizing hemorrhagic encephalopathy and is rare in multiple sclerosis and Schilder's disease. However, it was observed in the spinal cord in one case of subacute multiple sclerosis. Subependymal demyelination outside the lateral ventricles on the other hand is most evident in multiple sclerosis but also occurs in acute disseminated encephalomyelitis and in acute necrotizing hemorrhagic encephalopathy. It is rarely observed in Schilder's disease except where the massive degeneration of the central white matter extends to the wall of the ventricle.

Necrosis of blood vessels and of nervous tissue together with exudation of fibrin and inflammatory cells and hemorrhage is regularly observed in acute necrotizing hemorrhagic encephalopathy. It is rare in the other demyelinative diseases but in Case 14, in which an acute demyelinative process was found in the brain, there was a necrosis of the spinal cord. Also in Case 3 a necrotic cord lesion was associated with a demyelinative lesion in the optic nerve. Acute disseminated encephalomyelitis may at times result in vascular damage, exudation of fibrin, and necrosis of the tissue, as in Case 11. A necrotizing lesion may also occur in Schilder's disease.

Infiltrations of inflammatory cells in the perivascular spaces of Virchow-Robin occur in all four types of demyelinative diseases. The type of the cell is the same in all, being chiefly lymphocytes with some plasma cells and histiocytes, although in the acute necrotizing lesions neutrophilic leukocytes predominate. Focal meningitis is an invariable part of the pathology of acute necrotic hemorrhagic encephalopathy, and acute disseminated encephalomyelitis, and may be observed in acute multiple sclerosis.

The minute histology of the lesions in all four diseases is similar in many respects. Microglial activation occurs early and macrophages are found if a sufficient interval of time elapses between the onset of the disease and death; cellular and later fibrous gliosis represent the healing or healed stages of all diseases. Also the degenerating myelin is phagocytized and converted into fat, as in any disease which destroys myelin. Only in metachromatic leucoencephalopathy is there a departure from this pattern, with the

TABLE I

TABULATION OF THE PATHOLOGIC CHANGES IN THE DEMYELINATIVE DISEASES

	Multiple Sclerosis		Acute Disseminated Encephalomyelitis	Schilder's Disease	Metachromatic Leucoencephalopathy	Acute Necrotizing Hemorrhagic Encephalomyelopathy
	Acute	Chronic				
Location	Brain, brain stem, spinal cord, optic nerves (one or more)	Entire CNS* as a rule	Usually entire CNS, sometimes restricted to brain or cord	Cerebral white matter, optic nerves, ? rarely brain stem	Cerebral white matter, optic nerves ?	Cerebral white matter, brain stem, rarely cord
Distribution	Patchy, irregular	Patchy, irregular	Diffuse	Diffuse or uneven and asymmetrical	Diffuse, symmetrical	Usually symmetrical in one focus
Age of lesions	Different	Different	Uniform	Different	Different	Same
No. and extent of lesions	Few to many	Usually numerous and extensive	Usually innumerable and extensive	Few, extensive	Extensive global involvement	Many small confluent lesions in one large focus
Size	1 mm. or less to 5 or 5+ cm.	1 mm. or less to 5 or 5+ cm.	0.1 to 1 mm.	Large, often affecting most of cerebral white matter	Extensive global involvement of cerebral white matter	0.1 to 1.0 mm. in large confluent lesion
Relationship to:						
Veins	Prominent	Usual in some regions	Always and chiefly	Sometimes, not usually	0	Usual
Pia	Rare	Rare ?	Usually or always, often pronounced	0	0	0
Ependyma	?	Usual	Often	?	0	0
Degeneration of axis cylinders	Slight	Slight to moderate, rarely severe	Slight to severe	Moderate to severe	Severe	Mild to severe
Oligodendroglia	Restricted to lesion	Restricted to lesion	Restricted to lesion	Restricted to lesion	Severe; may precede demyelination	In lesion
Nerve cells	Not severe	0 or slight	0 or slight	Slight to moderate	Slight to moderate	Commonly in brain stem and cord lesions
Tissue necrosis	Not severe or extensive	Never severe or extensive	Infrequent	Slight to pronounced	0	Usually severe
Perivascular infiltration	Always marked	Usually, but not marked	Usually, slight to marked	Usually	? with metachromatic bodies but 0 inflammatory cells	Pronounced
Meningitis	Slight or none	0 or slight	Slight to moderate	0	0	Pronounced, largely neutrophilic
Degeneration of blood vessels	None	0	Rare	0	0	Constant and severe
Hemorrhage	0	0	Rare punctate probably agonal	0	0	Pronounced

* CNS = central nervous system.

formation of unusual catabolic products which exhibit a metachromatic staining tendency. If metachromatic leucoencephalopathy and acute brain purpura which appear to be different types of disease, are set apart, it is evident that the boundaries between the demyelinative diseases, as represented by acute and chronic multiple sclerosis, optic neuromyelitis, acute disseminated encephalomyelitis, acute necrotizing encephalomyelopathy and, at least, some of the cases of centrolobar sclerosis of the Schilder's type, are often poorly defined. Indeed, in any large group of cases of the demyelinative diseases there are always some which cannot be classified with certainty because they possess characteristics of two or more groups. These latter cases are of the utmost importance because they provide links between the different demyelinative diseases.

The Nature of the Demyelinating Diseases as Inferred from Morbid Anatomy. As stated in the introductory remarks it is doubtful whether demyelination is ever the sole effect of any disease. It occurs not only in the group of diseases under discussion but in various other dissimilar conditions such as anoxic encephalopathy and incomplete infarction. It would seem that the myelin sheath is particularly susceptible to injury by various processes and the finding of demyelination provides relatively little information as to the nature of the disease.

While it is true that in the demyelinative diseases axis cylinders, nerve cells and interstitial tissue may escape serious or extensive damage there are notable exceptions. Thus in multiple sclerosis certain symptoms such as serious impairment of vision following retrobulbar neuritis may be permanent and, as in Cases 3 and 4, many or all of the axis cylinders and on occasion even the supporting tissue may be destroyed. The same is true of acute disseminated encephalomyelitis and even more so of Schilder's disease, while perivascular necrosis is a cardinal feature of acute necrotizing hemorrhagic encephalopathy. Thus there are indications that the disease process responsible for demyelination may under certain circumstances result in a partial or total degeneration of other structures and even tissue necrosis. It is as if demyelination were the earliest or least intense expression of the disease. The concept that these diseases are due to a primary disorder of the myelin sheath, as some have suggested, does not seem tenable. Instead the process should be regarded as a focal necrobiosis which may vary in severity from simple demyelination through increasing degrees of damage to destruction of both myelin sheaths and axis cylinders to total necrosis of all elements. However, the localization of these lesions in the white matter of the brain and spinal cord suggests that some property of myelin is a determining factor in their pathogenesis. Most of the glial cell changes are secondary to this focal necrobiosis but the occurrence of a pronounced microgial proliferation before significant degeneration of myelin, as in Case 6, may have special significance. It is reminiscent of the early infiltration of histiocytes in the allergic (tuberculin) type of skin lesion.

Perivenous degeneration is another outstanding feature of these diseases. From our pathologic data there is reason to believe the periventricular and subpial degeneration in multiple sclerosis and acute disseminated encephalomyelitis are also related to subependymal and meningeal veins. It is remarkable that the periventricular lesions are located in the walls of the lateral and some parts of the third ventricles, where fiber tracts lie in apposition to the numerous medium-sized and large subependymal veins, and not in the aqueduct of Sylvius, fourth ventricle or the central canal of the spinal cord where there are very few veins. This suggests that the relationship of the lesions to the ependyma and the pia is more or less incidental. The remarkably uniform perivenous localization must have a special meaning but no explanation for it has been forthcoming.

The other pathologic finding which deserves emphasis is the perivascular exudation of inflammatory cells which is found in all but the most chronic lesions. The accumulations of lymphocytes, plasma cells and histiocytes are almost as typical as the perivenous necrobiosis. It can be stated with certainty that they are not secondary to the degeneration of myelin, as has been claimed, because they are not found regularly in other conditions in which myelin is destroyed. The most common cause of marked perivascular infiltration is infection but the other pathologic findings do not resemble those of any known infectious disease. Allergy is another recognized cause. In both infections and allergic diseases lymphocytes, plasma cells and histiocytes are believed to play a role in the formation of antibodies.

These morphologic changes are common to all

the diseases under consideration and this fact alone suggests that the pathogenesis must be similar. There are admittedly important differences in the clinical course. Some, such as acute disseminated encephalomyelitis and acute necrotic hemorrhagic encephalomyelopathy always occur as an acute, self-limited disease with little or no tendency to relapse whereas others are chronic and either progressive as Schilder's disease or remittent as multiple sclerosis. These differences may depend, at least in part, on the time sequences of the pathogenetic mechanism.

Numerous hypotheses as to the cause of these diseases have been proposed. Marburg and later Weil and Brickner postulated the existence of a lipolytic ferment which attacks the myelin sheath directly. Steiner claimed to have demonstrated spirochetes in some of the lesions of multiple sclerosis. Many different workers have suggested a viral etiology. Putnam and his associates have stated that the cause is venular thrombosis due to an increased clotting tendency of the blood. More recently the hypothesis of an allergic mechanism has been advanced.

Any satisfactory working hypothesis must take into account the pathologic changes and in particular the perivenous necrobiosis and the perivascular infiltrates of inflammatory cells. Many of the proposed theories fail to do so and for this reason alone almost surely are incorrect. There is, for example, little likelihood that the diseases are of infective origin because they do not show the pathologic changes characteristic of the known infectious diseases of the nervous system. It may be added that no infective agent has been demonstrated histiologically or by culture or animal inoculation. The chief argument against the theory of a metabolic disorder or the direct action of an enzyme on the nervous tissue is the presence of the infiltrates of inflammatory cells which are not seen in any of the known metabolic disorders of the brain. The hypothesis of venular thrombosis is not acceptable because the most careful search fails to reveal thrombosed vessels. It would be impossible not to see them in material like that of Case 11 if any were present. Moreover in cases of proved venous thrombosis the lesions have not resembled those of the demyelinative diseases.

The analogy between the main pathologic findings in certain of the demyelinating diseases and that of experimental allergic encephalomyelitis has suggested allergy as a likely mechanism. Certainly there is a striking similarity between the experimental disease and acute disseminated encephalomyelitis and acute necrotizing hemorrhagic encephalopathy as shown by Rivers, Sprunt and Berry,[42] Ferrara,[17] Wolf, Kabat and Bezer,[54] Morrison[37] and others. Furthermore, in some of the more chronic animal experiments the lesions have resembled acute multiple sclerosis both in type and distribution. These hypotheses will be evaluated more critically in another part of this symposium. It may be said that the morbid anatomy of the demyelinative diseases favors the allergic theory, a point of view which has previously been expressed by Ferraro[18] and others.

SUMMARY

A demyelinative disease is one in which there is destruction of myelin sheaths with relative sparing of axis cylinders, nerve cells and supporting tissues, occurring usually in multiple foci within the central nervous system. The diseases which conform to these criteria are acute and chronic multiple sclerosis, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic encephalomyelitis and Schilder's diffuse periaxial encephalitis. Brain purpura and metachromatic leucoencephalopathy resemble the demyelinative diseases in some respects but because of significant pathologic differences probably should not be included in the group. The pathology of these diseases is described. Each of the demyelinative diseases exhibits distinctive pathologic changes from which the diagnosis can usually be made without difficulty. There are, however, rather impressive similarities that may be overlooked. The essential process in these diseases is a focal necrobiosis of nervous tissue which varies in degree from degeneration of myelin sheaths with sparing of the axis cylinders to an almost complete degeneration or necrosis of all elements of nervous tissue. Common to all of the demyelinative diseases is a tendency for this focal necrobiosis to occur in relation to small veins and to involve the white matter in particular. This latter feature suggests that some property of myelin determines the localization of the pathology. Exudates of inflammatory cells in the perivascular spaces is another important feature. Theories as to the etiology and pathogenesis of these diseases are evaluated in the light of the morbid anatomy.

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Experimental Demyelination in Relation to Human and Animal Disease*

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Some years ago I[1] reviewed the then current knowledge of demyelination as a morbid process rather than as a feature of the spontaneous demyelinating diseases of man and animals. Even at that time the known antecedents of demyelination and the means by which it could be produced in the laboratory were very diverse, and they have been added to since. The observer surveying the whole field of comparative and experimental pathology, rather than focussing on a particular disease such as multiple sclerosis, could not but conclude that demyelination is simply the response characteristic of a particular tissue, the white matter of the brain and spinal cord, to injuries short of those rapidly lethal. As a corollary it seemed rather unlikely that a single etiologic agent or mechanism would be incriminated in all cases of human and animal demyelinating disease, or that the demyelination obtained under purely experimental conditions would necessarily point to the etiologic factors or mechanisms involved in man. Since then Ferraro[2] has sought to unify all human demyelinating diseases as expressions of an allergic reaction on the part of the nervous system. Again, by the application of new technic, our knowledge of the encephalomyelitis resulting from injection of nervous tissue has been greatly enhanced and new information has accrued in other directions. It is the purpose of the present article to consider the implications of this recent work, and particularly its possible bearing upon the pathogenesis of spontaneously occurring disease.

Disseminated Encephalomyelitis Following Injections of Nervous Tissue

In 1907 von Pirquet[3] expressed the belief that allergic phenomena normally play a part in the reaction of the body to vaccine virus, and that the rapid increase in size, between the eighth and twelfth days, of the areola surrounding the cutaneous papule indicates a reaction in the tissues between the antibodies then being formed rapidly and the virus in the papule. When post-vaccinal encephalitis became relatively common in the 1920's, Glanzmann[4] suggested that it might be allergic in origin; this hypothesis was developed by others and notably by Finley[5] while, as we have seen above, Ferraro[2] has since extended its scope to embrace all human demyelinating disease.

The fact that occasionally during the course of or following antirabic treatment an encephalomyelitis of the post-vaccinal type arises (Hurst[6] and Jervis, Burkhart and Koprowski[42]) led to attempts to reproduce the condition by repeated injections of normal brain tissue. In this way Hurst[6] produced paralysis in four of forty-three rabbits, but found in the brain, spinal cord or peripheral nerves no histologic changes which would account for the symptom. It may be mentioned that others[28,34,49] have also at times failed in the rabbit to correlate symptoms with lesions, although disseminated encephalomyelitis may undoubtedly be evoked in this species by injections of brain.[35]

Rivers and his colleagues,[7,8] on the other hand, produced nervous signs and lesions in the majority of monkeys injected over a period of months alternately with aqueous suspensions and alcohol-ether extracts of normal rabbit brain. The pathologic changes were characterized by demyelination occurring in relation to the blood vessels although in advanced lesions this relationship might be obscured. They were more severe in the white matter and especially in the pons, cerebellum and periventricular areas. The spinal cord was seldom affected. Thrombi were not observed. Eosinophilic infiltration played a part in the cellular changes; multinucleated giant-cells and "globoid cells"

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developed at an early stage and were followed by numerous granular corpuscles. Fragments of broken myelin sheaths often appeared like large bacteria or as globules within phagocytic cells.

While Innes and Shearer[9] and Hurst[1] using various heterologous brains over periods of up to a year were unable to reproduce these lesions in sheep, monkeys or rabbits, Ferraro and Jervis[10] were more successful. After receiving 29 to 103 injections in from 112 to 405 days, their monkeys developed progressive nervous symptoms and at autopsy presented changes essentially similar to those described above. In addition to the perivascular demyelination two brains showed large areas of partial destruction of myelin bearing no obvious relation to the vessels. At the periphery and sometimes in the center of the lesions the macroglia was hypertrophied and hyperplastic, and again many giant cells were present. The occurrence of giant cells in various demyelinating conditions in man has been noted by a number of authors (Ferraro[2]), and has even been considered as representing a neoplastic feature. Ferraro[2] has expressed the view that, in general, insufficient attention has been paid to this histologic detail which he regards as an important link between the human and the experimentally produced diseases. Like those of Rivers et al., the brains of Ferraro and Jervis' monkeys showed no thrombi or emboli.

Morgan[11,12] made an important contribution to technic when she observed that monkeys injected twice or thrice with homologous nervous tissue plus adjuvants (paraffin oil and tubercle bacilli), according to the method of Freund and McDermott,[13] developed widespread encephalomyelitis within the much shorter time of two to seven weeks. Cerebral white matter and spinal cord were highly effective and produced disease in eight of ten and sixteen of twenty-one animals, respectively, the former after a shorter period than the latter. Grey matter containing an estimated 10 per cent of white matter was far less effective, and peripheral nerve, kidney and saline solution ineffective. The brains of affected animals displayed abundant petechial hemorrhages and occasional large patches of hemorrhagic softening. The illustrations of the macroscopic lesions are reminiscent of the acute hemorrhagic leukoencephalitis described by Hurst and others,[14–18] and more remotely of the epizootic leukoencephalitis of horses reported by MacCallum and Buckley and others[19–21] and believed to be caused by feeding moldy corn.[22] Microscopically, intense perivascular and extravascular infiltration with mononuclears, polymorphonuclears and eosinophils was widespread in the brain and less severe in the cord. More severely affected areas showed focal necrosis and hemorrhage with demyelination at the periphery of the lesions. The giant cells described by Rivers and Schwentker[8] and Ferraro and Jervis[10] were wanting in this more acute encephalomyelitis.

Working independently, Kabat, Wolf and Bezer[23–25] confirmed these findings with both homologous and heterologous (rabbit) brain; in two monkeys a single injection sufficed to evoke nervous disease. Rabbit lung and fetal (myelin-free) rabbit brain were ineffective. In these cases lesions were most severe in the brainstem and cerebellum, and the reader obtains the impression that demyelination was relatively more marked and hemorrhages and necrosis less intense than in Morgan's animals. The focal lesions were related more particularly to venules, veins and capillaries. In the more acute lesions, polymorphs (and on occasion fibrin) infiltrated the walls of the vessels and often extended into the surrounding nervous tissues. Pericapillary hemorrhages occurred and in places coalesced into large areas. Perivascular zones of demyelination often united to form large demyelinated plaques of fuzzy or sharply cut outline, but axons were relatively well preserved. After three to four days increasing numbers of lymphocytes and large mononuclear cells derived from the adventitia occupied the perivascular spaces, and still later broad collars of epithelioid cells mingled in the extravascular areas with rounded microglial phagocytes containing fragments of degenerating myelin. There were no giant cells. At these later stages acute lesions might be superimposed on the more chronic changes in particular areas, and the authors associate this mixture with the striking tendency to remissions and recurrences of the clinical manifestations of the malady. They were able to discern many points of resemblance to multiple sclerosis, disseminated encephalomyelitis and diffuse sclerosis in man.

By diminishing the doses of brain and of tubercle bacilli, Ferraro and Cazzullo[26] produced in monkeys a more chronic nervous disorder remitting and relapsing over several months. In the brains of their animals subacute

inflammatory phenomena persisted. A patchy demyelination, with a few areas of frank necrosis, was present in all areas of the cerebral white matter; in the spinal cord, on the other hand, the myelin was diffusely rarefied. The glial reaction in the brain was similar to that in human demyelinating diseases but less than in multiple sclerosis, while in the spinal cord the typical gliosis of multiple sclerosis was not observed.

Essentially similar fatal or non-fatal nervous complications have been induced after a relatively constant "incubation period" in nearly mature guinea pigs[27–34,40,64] (but not so easily in baby guinea pigs[28–30]) with one or more injections with adjuvants of fresh or phenolized guinea pig, rabbit, human, caprine, bovine or porcine, but not rat[34] brain. In the guinea pig the disease may show remissions and relapses, and animals recovered from previous symptoms may develop them anew when re-injected months later.[30] Apparently, however, animals completely resistant to one course of injections also resist a second course.[34] The rabbit is susceptible to homologous brain[35] and possibly to rat brain,[28] the monkey to monkey, chicken or human, but not frog or fish brain.[36] A monkey's own brain may serve.[37] In the mouse homologous brain tends to produce a chronic, relapsing type of disease accompanied by bouts of asthmatic breathing,[38] with marked differences in incidence in various strains;[39] these differences may be the equivalent of familial susceptibility (or the reverse) to demyelinating disease in man. The rat, an animal not easily sensitized,[56] has proved refractory over periods of up to nearly a year to homologous and to guinea pig and rabbit brain.[28,34] After repeated injections over a period of months the dog[41] often develops symptoms rather suddenly within a fairly constant interval of time (6–15 and mostly 6–9 days) following the preceding injection; as in post-vaccinal encephalitis in man a severely paralyzed animal may make a rapid recovery. Multiple relapses frequently follow subsequent injections. All the foregoing work stresses the importance of combining the suspension of brain with adjuvants, and in the dog many injections may be necessary. Yet in one breed, Jervis, Burkhart and Koprowski[42] observed four cases of paralytic accident with severe and widespread demyelinating lesions among sixty dogs treated with a solitary dose of phenolized antirabic vaccine containing no adjuvants, possibly again indicative of marked differences in susceptibility between strains of animal. Some workers[30,36] have failed to affect guinea pigs or monkeys with suspensions of homologous or heterologous nerve, but Lumsden[34] succeeded with homologous peripheral nerve in the guinea pig as did Alvord[29,30] with optic nerve. With one possible exception,[28] however, no one has produced encephalomyelitis with homologous or heterologous serum,[27] cardiac[27,30] or skeletal muscle,[34] kidney,[27,30,34,64] liver,[28,34,64] pancreas,[30] spleen,[64] testis,[28,30,64] adrenal,[64] placenta[64] or neoplasm[30] and only very doubtfully with skin.[64]

Without devoting inordinate space to the minutiae of histopathology, it may be stated that in the dog the lesions in the nervous system are more closely akin to those in the monkey than are the changes in guinea pigs, rabbits or mice; demyelination is more prominent and actual cavitation from loss of tissue has been described.[41] Nevertheless, most authors regard lesions in the guinea pig, etc., as the equivalent of those in the monkey; they are closely related to the blood vessels of meninges and parenchyma, with particular emphasis in the white matter where perivascular demyelination may occur. Lumsden[34] makes the point that whereas any involvement of arteries and arterioles is of "banal lymphocytic character," that of the venules consists predominantly in concentric proliferation of the adventitial cells, which tend to obliterate the Virchow-Robin spaces. (This apparently is the change to which other writers, e.g., Alvord and Stevenson,[58] refer as granulomatous thickening.) Associated with this change are microglial proliferation and demyelination in the extra-adventitial tissues. In these respects the lesions reproduce the appearances of post-exanthematous encephalitis of man. In Lumsden's animals the lumina of affected vessels were never narrowed, rather were the vessels engorged and distended; others[27,33,40] have observed occlusion due to thickening of the wall or to thrombosis. Since prolonged treatment with dicumarol[52] does not influence the incidence of encephalomyelitis, the latter cannot be a vital pathogenetic factor. The more acute lesions may be accompanied by hemorrhage.[27,40] Opinions diverge on whether or not the cord is less affected than the cerebrum; vascular lesions may be present in the nerve roots[27,40] but not in the peripheral nerves.[34,40] It remains to be added that these changes have been found in

animals exhibiting no visible signs of disease, and that in those presenting symptoms the changes have varied greatly in intensity from individual to individual and in different experiments.

Freund, Lipton and Morrison[43] obtained a chronic condition in some guinea pigs by using in their emulsions Myco. butyricum grown without glycerin to reduce its acid-fastness. The animals which were killed as long as 182 days after the onset of paralysis showed much more pronounced demyelination, especially around the periphery of the spinal cord, with conspicuous preservation of the axons and little or no gliosis but marked thickening of the vessel walls from deposition of reticulum fibers. In chronic cases Alvord and Stevenson[58] described both gliosis and fibrosis in the demyelinated areas.

As we have seen, all this work originated from the thesis that post-vaccinal and pathologically similar forms of encephalitis result from an allergic reaction occurring in the course of the acute exanthem or during antirabic treatment. The production of encephalomyelitis, first by repeated injection of brain suspensions and later and more rapidly and consistently by brain combined with adjuvants known to enhance the development of immunity to a variety of antigens, at once convinced many workers of the validity of the working hypothesis and led to use of the term "allergic" or "iso-allergic encephalomyelitis" to designate the experimental condition. Since a diagnosis of allergy presupposes an antigen and an antibody, it led also to efforts to detect these two essential components of the reaction.

Attempts to define the substance or substances in brain responsible for evoking these changes have not reached finality. From what has gone before it is clear that the encephalitogenic factor is organ- rather than species-specific, and is most abundant in the white matter of the brain (with Lumsden[64] dissenting). It is usually absent from fetal and neonatal brain[30,36] but the immediately prenatal (and relatively mature) guinea-pig provides an exception.[64] It resists boiling and autoclaving[23,30,36,64] and fixation in formalin.[35,36,64] Brain in which lecithin has been hydrolysed with Cl. welchii toxin is still effective[35] as were alcoholic extracts in the hands of some[28] but not all[36] workers. Alvord[29,30] found activity in the phosphatide fraction, but none in cholesterol, "protagon," cerebrosides and sphingomyelin, or the protein fraction after extraction of all lipoids. Koprowski and Jervis,[32] however, claimed that the last two mentioned were effective, Lumsden[64] that the cerebroside-sphingomyelin fraction was active, and Ferraro, Roizin and Cazzullo[44] that several lipoid fractions and the protein residue were all capable of producing disease in guinea pigs but that no individual fraction possessed antigenic properties as strong as those of whole brain. Bell, Wright and Habel[45] and Hottle, Nedzel, Wright and Bell[46] described the separation of an active fraction in a biuret-negative dialysate through a cellophane membrane; they estimated its molecular weight at less than 10,000. Many of the properties of this substance appear to be shared by the anaphylactogen detected in nervous tissue by Bailey and Gardner[47,48] and at first believed by them to be a polysaccharide or protein and later a derivative of neurokeratin. The anaphylactogen, however, was of higher molecular weight and did not diffuse through a cellophane membrane; moreover, neurokeratin prepared by the method of Bailey and Gardner did not cause encephalomyelitis.[28] Ferraro and Roizin[65] have recently evoked encephalomyelitis with a calcium acetate-protein compound prepared by Bell. Waksman and Morrison[52] failed to confirm the work of Hottle et al. and ascribed antigenic effectiveness to a fraction insoluble in water and ether, and possibly related to the proteolipid A of beef brain. There for the moment the matter rests; it would seem of the greatest importance that further attempts should be made to characterize the active factor if we are to understand fully the mechanism by which encephalomyelitis is produced.

The search for an antibody has been equally inconclusive. It has long been known that brain-specific antisera can be obtained by injecting animals with suspensions of heterologous brain, or with alcoholic extracts of homologous or heterologous brain "conveyed" by a suitable protein.[1,50] The various sera so prepared react in the complement-fixation test with suspensions and with alcoholic extracts of the brains of all species tested, so that like the encephalitogenic factor the brain antigen is organ- rather than species-specific. Suspensions of normal homologous brain are not antigenic in this manner but Schwentker and Rivers[49] showed that autolysis or disease (vaccinial infec-

tion) could so alter the nervous tissues as to render them antigenic when inoculated into the same species. Like the encephalitogenic factor, the specific brain antigen is much more abundant in white matter than in grey; in amount it appears to parallel the development of myelin in the maturing animal.[49] Some[32,40,41,51] but not all of the observers who have produced encephalomyelitis by injection of brain with adjuvants have demonstrated the presence of complement-fixing antibodies in the sera of their animals; indeed several antibodies of this kind may be present[40,51] which is not perhaps surprising when we remember the complexity of the antigen. There exists, however, no exact correlation between the presence or absence of such antibodies and the development of encephalomyelitis,[28,40,41,51] while in Jervis, Burkhart and Koprowski's series of paralytic accidents in dogs[42] no complement-fixing antibodies were detected. This lack of correlation may merely signify that after all, in spite of the resemblances mentioned above, the encephalitogenic factor is distinct from the antigen responsible for stimulating the development of complement-fixing antibodies, or, to quote the words of Thomas, Paterson and Smithwick,[41] that "the antibody in dog serum may represent an immunological event which is irrelevant to the condition" (encephalomyelitis).

The results of skin tests by the earlier workers[27,28] were also not clearly related to the nervous disease and were positive only when heterologous brain had been used. Thus guinea pigs receiving rabbit brain reacted when tested with rabbit but not with guinea pig brain, whereas those given guinea pig brain reacted with neither,[28] yet guinea pig brain functioned as well as did rabbit brain in inciting encephalomyelitis. Recently, however, Waksman and Morrison[52] have demonstrated that in the rabbit homologous spinal cord induces dermal reactivity characteristic of the response to tuberculin, and that both in degree and time this state of reactivity coincides closely with the incidence of encephalitis. How a sensitivity of this type directed at some neural constituent results in encephalomyelitis was not explained, although the authors considered the possibility of transfer of antibody across the blood-brain barrier by cellular agency (see Morrison,[35] Dougherty et al.,[53] Chase[54] and Kopeloff and Kopeloff[55]). Under these circumstances the investigator would not necessarily expect to find the relevant antibody in the blood stream, and in fact all have failed who have tried to reproduce the demyelinating encephalitis by transfer of even massive doses of serum intraperitoneally, intravenously or intracisternally from encephalitic to new animals,[12,27,36,40] although Hurst and Atkinson[1] obtained widespread meningitis and choroiditis by intrathecal inoculation in pigs of various antisera to brain tissue. Equally fruitless were attempts to reproduce the demyelinating condition by intraperitoneal or intramuscular injection of peritoneal exudates, spleen or lymph nodes;[36,40] intracisternal injection of cellular material apparently has not been carried out.

Kabat et al.[36] explained their inability to induce encephalitis by transfer of serum by assuming a continuous fixation of antibody by antigen present in the nervous tissue of the donor animal. This explanation would imply a degree of permeability of the blood-brain barrier to antibodies greater than that likely to exist (Morgan et al.[57]) or, if in the presence of encephalomyelitis such permeability does exist, would then raise the question of how complement-fixing antibodies to nervous tissue sometimes persist in the blood stream as they are known to do.

A few efforts have been made to prevent the encephalomyelitis resulting from injections of brain plus adjuvants. Ferraro, Roizin and Cazzullo[44] diminished morbidity and mortality by injecting also massive or repeated smaller doses of brain without adjuvants. The former they assumed to act as a "substitute brain" deflecting antibodies from their usual destination, the latter as a desensitizing regimen. Good, Campbell and Good[59] observed a prophylactic effect of large doses of sodium salicylate, an effect increased by simultaneous exhibition of para-aminobenzoic acid. Sodium salicylate is known to inhibit or diminish various reactions of hypersensitivity.[60–62] ACTH also prevents the development of encephalomyelitis.[63]

Thus although the postulated antigen and antibody have not finally been identified, and the detailed mechanism by which the nervous lesions are produced awaits discovery, a good deal of circumstantial evidence favours the view that the encephalomyelitis following injections of brain tissue is the expression of an allergic reaction. It is with some difficulty perhaps that one fits into this general picture the observations of Vogel.[85,86]

From time to time various workers have examined the action of substances with hemolytic activity in producing demyelination when incubated *in vitro* with pieces of spinal cord. Claims have also been advanced and rejected of abnormal myelolytic or lipolytic activity of the serum or urine in cases of multiple sclerosis.[1] Morrison and Zamecnik[83] demonstrated *in vitro* that the myelin sheath can be broken down by several enzymes (Cl. welchii α toxin, cobra venom, etc.), and this in more than one way chemically, thus suggesting "that 'demyelination' may not always be precisely the same process." They were unable, however, to produce clear-cut lesions by intravenous or intracerebral injections in rabbits, although Frazer et al.[84] claimed to have produced demyelination in the brain and spinal cord of guinea pigs by intramuscular injection of the α toxin, and to have observed it in two human cases of intoxication. Vogel,[85] on the other hand, obtained foci of demyelination, with little or no neuronal degeneration or inflammatory response, in the brains of rabbits inoculated intracerebrally or intravenously with purified lipase, and he alleged a resemblance of these lesions to those of multiple sclerosis. Moreover, he found that the lymph nodes of guinea pigs developing encephalomyelitis as a result of injections of brain tissue plus adjuvants contained large numbers of histiocytes with lipolytic enzyme in their cytoplasm.[86] If either brain tissue or the acid-fast organisms (Myco. butyricum) were omitted from the material injected, encephalomyelitis did not develop; under these circumstances scarcely any lipolytic enzyme existed in the lymph nodes. Combining his two sets of observations, Vogel suggested that the lipolytic enzyme may be a factor in the pathogenesis of the experimental encephalomyelitis. He makes no comment on the fact that the histologic changes produced by lipase appear to have been quite different from those in the experimental encephalomyelitis, nor does he appear wholly to have excluded the possibility that the development of lipolytic enzyme may, like that of complement-fixing antibodies, be a concomitant rather than a determinant phenomenon.

In thus reviewing the very large volume of work already carried out on this subject, we are obviously confronted with a picture of which the broad outlines have been sketched while several essential details remain to be filled in; it is important that overenthusiasm for what has already been accomplished should not induce us to fill in the gaps in a manner which will confuse the painters, present and future. However, before we discuss the probable interpretations to be placed upon this work, and the significance of the new knowledge for the student of human disease, we may consider briefly the other contributions made in recent years to the subject of experimental demyelination.

MISCELLANEOUS ANTIGEN-ANTIBODY REACTIONS IN THE CENTRAL NERVOUS SYSTEM

Reactions of hypersensitivity to various antigens have occasionally been studied in the nervous system. Some clinical states believed to originate in reactions of this nature, together with the earlier experimental work, have been reviewed more fully elsewhere;[1] Kennedy[66] has recently emphasized again the existence of the former. The experimental work has been concerned mainly with the occurrence in the brain of the Arthus phenomenon following intracerebral injection of an antigen (horse-serum or egg-albumin) into a previously sensitized animal. The resulting localized lesions have been highly hemorrhagic, with edema, vascular thrombosis, abundant polymorphonuclear exudate and central necrosis of tissue; these lesions Alexander and Campbell[67] considered to differ only quantitatively from those evoked by the antigen in non-sensitized animals. Jervis, Ferraro, Kopeloff and Kopeloff[68] described additional and more remote lesions in monkeys which had received dozens of intracerebral doses of antigen. These lesions took the form of areas of demyelination exhibiting giant cells and other features similar to those following multiple injections of brain suspensions and extracts.[10] The authors supposed that these changes were due to the action of brain-specific antibodies, formed in response to a complex antigen composed of foreign protein united to a hapten derived from the myelin damaged by repeated intracerebral inoculations.

Koprowski and Jervis[32] found that guinea pigs treated with heterologous brain emulsion and adjuvants, but failing to develop encephalomyelitis, reacted violently to intracerebral injection of a suspension of heterologous brain. Those dying within a few days showed the usual necrotic and hemorrhagic lesions of the Arthus phenomenon, but in others surviving a

week or more local demyelination was the chief feature at the site of inoculation; in addition, numerous disseminated areas of demyelination were scattered throughout the central nervous system.

Jervis[69] investigated the neurologic disturbances forming the basis of the "carotid syndrome" of Forssman. The tissues of the guinea pig normally contain the Forssman antigen. If a serum containing Forssman antibodies is slowly injected centripetally into a carotid artery ligated distal to the point of injection, very marked changes ensue. The antigen-antibody reaction occurring in the vessel walls of the homolateral medulla, pons and cerebellum damages them and makes them permeable to substances which normally do not pass the blood-brain barrier, including, presumably, the antibodies. In animals surviving for several days, Jervis found in the affected areas many sharply defined foci of demyelination (multiple degenerative softenings) and slighter alterations in nerve cells and glia; the lesions did not depend on vascular thrombosis or embolism. Injected intracerebrally the same sera produced changes characteristic of the Arthus phenomenon.

Good[70] has recently studied the cytologic details of the inflammatory response to intracerebral injection of antigen in sensitized and non-sensitized animals. In the former not only were necrosis and hemorrhage much more conspicuous, but the early development of numerous "plasma-cell polyblasts," and later of mature plasma-cells, served to differentiate the acute allergic from the non-allergic reaction.

The present interest of the foregoing work is in offering a choice of antigens, each of which will evoke similar nervous changes in the sensitized animal, and in linking the more acute hemorrhagic necrosis of the Arthus phenomenon with the demyelinating lesions which may arise in animals dying less abruptly.

ANOXIA, VASCULAR BLOCKAGE AND DEMYELINATION

Conspicuous demyelination may follow a variety of procedures which in one way or another interfere with the normal oxidative requirements of the cell.

Ferraro[71] produced repeated bouts of histotoxic anoxia by doses of potassium cyanide at levels nearly approaching the lethal. In cats and monkeys there resulted demyelinating lesions very similar in distribution to those of diffuse sclerosis. Several authors confirmed these observations, particularly Hurst[21,72] who analyzed the precise conditions under which demyelination occurs and showed that in monkeys the effects of the poison differ materially according to the dosage. Thus massive single or repeated doses damaged chiefly the cerebral or cerebellar cortex, while repeated (less often single) rather smaller doses led to bilateral necrosis in the basal ganglia or cerebral white matter, or both. Necrosis often developed suddenly and simultaneously in a remarkable manner over wide tracts of the white matter after a dose of poison previously tolerated on many occasions. The areas affected included the centrum semi-ovale, corpus callosum, anterior commisure, and so on, with smaller lesions lying centrally in the projections of white matter into the cerebral gyri. Since cyanide is rapidly destroyed in the body, these sudden catastrophes could not be attributed to progressive accumulation of drug; nevertheless, they occurred so constantly that it seemed that the *effects* of individual doses of the drug must be cumulative. Because today allergy occupies so prominent a place in discussions on the etiology of demyelination, it should be affirmed categorically that these sudden catastrophes did not have an allergic basis, since occasionally the same results followed a single exposure to cyanide.[21] In monkeys receiving repeated, still smaller doses over a longer period the grey matter usually escaped injury and lesions were confined to the white. They now took the form of severe demyelination, with much loss of axons, in the regions mentioned above; they tended to spare the U-fibers and still more the internal capsules and optic radiations. Lumsden[73] has described essentially similar changes in the rat and, like Hurst,[1] has compared them with those in the Marchiafava-Bignami disease.

With sodium azide also Hurst[72] found it possible, according to circumstances, to cause either demyelination or full necrosis in the white matter, although with this noxa damage was inflicted principally upon the optic nerves and tracts rather than upon the centrum semiovale. Necrosis in the optic connections might follow single large doses or might develop abruptly from the summation of the *effects* of many smaller doses each insufficient to cause marked disturbances; once more, in the latter event the sudden necrosis could not be explained on the basis of accumulation within the system

of the drug itself. Prolonged poisoning with small doses led to demyelination in the optic nerves and tracts.

The nature of the disturbance which leads cumulatively to necrosis or demyelination is as yet obscure. In experiments interrupted by the war Wyndham[72,74] failed to detect a biochemical basis, and Lumsden's suggestion[73] of a toxic or myelinolytic agent liberated *in situ* requires experimental evidence before it is more than an interesting hypothesis. That an indirect mechanism is concerned rather than the cyanide and azide themselves, receives confirmation from the work of Morrison.[77] Here simple anoxic anoxia induced by breathing atmospheres poor in oxygen, or alternatively by simulated high altitudes in a decompression chamber, produced practically all the different lesions ever reported by one or other writer to occur in the various types of anoxia. The variable factors in Morrison's experiments were those of intensity and duration of the anoxia. Demyelination in the cerebral white matter, closely resembling the milder degrees obtained in poisoning with cyanide, followed many daily and prolonged sessions of moderate hypoxia (10 or fewer volumes per cent of O_2 in the blood), while a single, sudden exposure to much more severe hypoxia resulted in extensive laminar necrosis in the cerebral cortex. Fatalities in man after exposure to simulated high altitudes[78] have also been accompanied by demyelination although the precise determinant in these cases was considered to be a matter of uncertainty.

Many pathologic accounts in man[1,75] and some experimental investigations[1] point to carbon monoxide as an occasional cause of more or less extensive demyelination of the cerebral white matter. In this instance prevailing opinion attributes the lesions to vascular spasm, vascular dilatation with stasis, thrombosis, etc., so that perhaps both anemic and stagnant anoxia are concerned in the pathogenesis. O'Brien and Steegman[76] have recorded necrosis in the parietal and occipital white matter after anesthesia with nitrous oxide, and Hurst[72] noted early changes in the white matter of monkeys given repeated large doses of barbiturates.

Finally, Putnam's well known views on the importance of venular thrombosis in the genesis of the plaques of multiple sclerosis have inspired a number of experimental studies both by Putnam and his colleagues, and by others; these have been reviewed fully elsewhere.[1] Suffice it at the moment to say that the more recent accounts of the sequelae of experimental microembolism and microthrombosis in the central nervous system[73,79] agree in the main with those relating to fat embolism in man;[80–82] relatively minor degrees of obstruction to the circulation in the white matter lead to areas of demyelination with destruction of the axons and more severe blockage to patches of frank necrosis. There are few who see in these lesions a replica of those in the more important demyelinating diseases in man although Hurst[1] has compared them to those in Binswanger's disease. Lumsden[73] in particular has contrasted the shrunken, poorly demarcated scars which represent the final stage of some of these lesions with the plaque of multiple sclerosis "découpée comme à l'emporte-pièce" in which the bulk of tissue is not affected. From the opposite direction, very many writers who have produced demyelinating lesions by a variety of measures have been at pains specifically to record the absence of thrombi or emboli at any stage of the process.

DEMYELINATION IN VIRUS INFECTIONS OF THE NERVOUS SYSTEM

For a time it was usual to classify cases of encephalitis as "polioclastic" in which a virus destroyed predominantly the grey matter and caused primary damage to the neurons, and "myelinoclastic" when the brunt of the attack was borne by the white matter and no convincing evidence of direct participation by a virus was forthcoming. Evidence accumulated during the last decade or so has progressively blurred the line of demarcation between these two varieties of encephalitis although, of course, the extremes in each category remain as far apart as ever.

In the "nervous form" of canine distemper lesions of the grey matter characteristic of the attack of a neurotropic virus may be seen in some parts of the central nervous system while in other areas (cerebellar white matter, brain-stem and elsewhere) demyelinating lesions closely resembling those in human disseminated encephalomyelitis obtain. The latter, first described adequately by Perdrau and Pugh,[87] are often the more conspicuous. Clinically, the nervous manifestations of distemper ordinarily become apparent several weeks after the catarrhal phase of the disease, and they may develop without obvious initial illness. Perdrau and Pugh, therefore, doubted the direct causal

relation of distemper to the disseminated encephalomyelitis in question, and regarded the latter as more nearly analogous to post-vaccinal encephalitis. On the other hand, Marinesco et al.[88] described the condition as a "leuco-polionévraxite" intermediate between those conditions excited by viruses destroying mainly the grey matter (poliomyelitis, rabies, etc.) and the post-vaccinal type of encephalomyelitis. Today, the combined picture might well be interpreted by some as evidence of an allergic encephalitis superimposed upon that resulting from the attack of a neurotropic virus. Careful re-study of material previously examined[89] suggests that this last view is not correct.

From their experimental work Hurst, Cooke and Melvin[89] concluded that the cause of the demyelination in disseminated encephalomyelitis of dogs is the distemper virus itself. Inclusions similar to those present in infections with known distemper virus were often seen in the lesions, and a virus indistinguishable from that of distemper was isolated from the brains of naturally infected dogs. In the brains of animals inoculated intracerebrally and intramuscularly either with nervous material from cases of encephalomyelitis or with known distemper virus early lesions characteristic of "nervous distemper" existed at the time of onset of systemic symptoms of distemper. Re-examination of this pathologic material has revealed in one or two cases changes which Ferraro would accept as evidence of a "hyperergic reaction," but these appeared exclusively in spontaneously occurring cases in which there was a history of illness preceding by two to six weeks the onset of nervous symptoms. In the experimentally produced disease examined at an early stage, the appearances were unequivocally those of a direct attack by the virus on the white matter, with no allergic component. Apparently the virus of canine distemper possesses an affinity for certain parts of the white matter more marked than that of most viruses affecting the nervous system. According to circumstances it may cause almost complete destruction of the white matter, which is then reduced to a mass of granular corpuscles, blood vessels and collagen, or it may be responsible for demyelination accompanied or not by destruction of the axons. King[96] contrasted these lesions with the foci occurring in a number of virus diseases[1] in which "the myelin disappears only as a part of the general tissue disintegration."

McIntyre, Trevan and Montgomerie,[90] Verlinde[91] and Innes[92] have since doubted whether the demyelinating encephalomyelitis of the dog is really caused by a typical distemper virus. While their challenge does not materially affect the present argument that demyelinating lesions may result from direct attack of a virus, it is of interest that the recent histopathologic and experimental findings in "nervous distemper" by Koprowski and his colleagues[93] duplicate exactly those recorded by Hurst, Cooke and Melvin. It may be that more than one virus is capable of causing demyelination in the canine brain and that the several groups of workers have dealt with different diseases.

Nor is the distemper virus alone in possessing an affinity for the white matter. From a case of spontaneous encephalomyelitis in a mouse, Cheever and his associates[94,95] isolated a virus pathogenic for mice, hamsters and rats. In mice the nervous lesions produced were of two kinds, predominantly necrotic in the olfactory bulbs and hippocampal region and characterized by widespread demyelination elsewhere. In the brain-stem and spinal cord areas of destruction of myelin sheaths and other tissue elements usually contained persistent and normal axons.

Again, in cases of subacute inclusion encephalitis in man severe diffuse demyelination may affect the white matter; and although opinions have differed as to its significance,[97,98] it remains a fact that inclusions have been noted in the oligodendroglia, suggesting a direct attack of the presumed virus on the tissue elements which are believed to subserve the nutrition of the myelin sheaths. That in some of these cases inclusions may be difficult to detect, and van Bogaert[99] has described a very similar pathologic state minus the inclusions, may lead one to suspect that the last word has not been said on the relation of viruses to demyelination in man.

COMMENTS—WITH SPECIAL REFERENCE TO THE RELATION OF ALLERGY TO DEMYELINATION

We have seen that strong circumstantial evidence points to allergy as the basis of the encephalomyelitis following injections of brain. Any hints of caution on the part of individual writers who have reached this conclusion have perhaps reflected the presumptive rather than the scientifically conclusive nature of the evidence so far available, and certainly have not offered a convincing alternative explana-

tion of the facts. Many authors have discerned resemblances between the experimental disease provoked in this manner and some of the more acute demyelinating maladies of man, while Ferraro[2] has proclaimed his belief in an allergic pathology of all the common human demyelinating diseases. Before considering the validity of his argument we may perhaps voice the opinion that our by no means exhaustive account of the measures by which demyelination may be brought about in the laboratory suggests that we are under no compulsion to envisage a single mechanism operative in all the naturally occurring demyelinating diseases of man and animals—of animals as well as man because obviously the problem should be viewed from the widest possible angle. The far from superficial differences existing between the various animal diseases relegated to this category are apparent from the summary of King and Meehan,[100] and it is clear that taken with the well known human maladies these animal diseases constitute a group of some heterogeneity.

If it be objected that some of the experimental procedures described in this review are highly artificial and unlikely to throw light on the problems of human and veterinary practice, we would readily agree that, let us say, poisoning with potassium cyanide can have little direct bearing in this connection. As we have shown, however, it is quite evident that as far as the lesions in the white matter are concerned the cyanide does not act *qua* cyanide, but that repeated bouts of anoxia from any cause gradually release destructive forces which, often quite suddenly, involve the white matter in the most serious consequences. That we do not yet know what precisely these destructive forces are makes it difficult to judge whether or not they are likely to be unleashed by other means or, in other words, to estimate how far the experimental observations are relevant or can be made relevant to human and animal disease.

We have mentioned previously that demyelination appears to be the invariable response of a particular tissue, the white matter of the brain and cord, to injuries short of those fully lethal, but we certainly do not know to what extent all naturally occurring demyelination proceeds in the same manner, chemically or otherwise. The current stains for myelin are conspicuously successful in providing a brilliant contrast between normal and demyelinated areas, but they reveal next to nothing of what is happening biochemically, and it may well be that wholly different processes lead to what, by crude histopathologic methods, appear rather similar end results. Both experimentally[83] and in human pathology[102] there are hints that this may be so. At present the lack of knowledge is so great that it would be most unwise to generalize broadly on inadequate evidence in order to fit inconvenient facts to a currently attractive hypothesis.

If with this attitude we approach the better defined demyelinating diseases of man and animals, we recognize a few for which an allergic basis seems a reasonable assumption. Such is the acute hemorrhagic leucoencephalitis which appears so obviously as the naturally occurring counterpart of the experimentally induced cerebral Arthus phenomenon. The acute epizootic leucoencephalitis of horses also may well fall into the same category. Furthermore, the balance of evidence is in favour of an allergic basis for the post-vaccinal type of encephalitis and for some of the paralytic accidents of antirabic therapy in man and in the dog, although it does not appear necessary with Schwentker and Rivers[49] to suggest that the post-infection group "is in some manner associated with the development of specific antibodies for brain." Even under conditions highly favouring the development of immunity, namely, when brain is injected combined with adjuvants, encephalomyelitis commonly takes three weeks to "incubate," whereas in post-vaccinal cases the peak of incidence is around the tenth to thirteenth day after vaccination. Moreover, after conventional vaccination there is no evidence that the virus attacks the human nervous system to render it antigenic in its own species as it can do in the rabbit inoculated intracerebrally. It seems much more likely that the antigen in post-vaccinal encephalitis is the vaccine virus, or perhaps less probably some product resulting from its attack on the skin[34] although the precise circumstances attending sensitization of the brain are still obscure. Experimental studies have disclosed very similar lesions in the nervous system whatever the antigen-antibody reaction involved.

On the other hand, the evidence that diseases like diffuse sclerosis, said not to be a homogeneous group of conditions,[101,102] and multiple sclerosis are allergic in origin depends very largely on the claim that histologic changes characteristic of "hyperergic reactions" are

present at some time in some of the lesions. But Jervis, Ferraro and the Kopeloffs[68] have demonstrated the possibility of animals becoming sensitized to products of breakdown of their own myelin, so that in a chronic condition characterized by progressive or remittent destruction of myelin a claim of this nature cannot carry the weight it would in a disease of abrupt onset and rapidly fatal course. Even in acute conditions, if we are to credit the accounts of recent cytologic studies, doubt may arise as to the significance of histologic changes believed to be characteristic of the allergic response. We have seen above how Good[70] differentiates acute allergic from non-allergic inflammation by the early appearance in the former of plasma cells and their precursors. Now Campbell[103] has maintained that in their *earliest* stages (to be exact as early as the fifth day after corneal inoculation) the lesions of acute herpetic encephalitis already display the cellular changes characteristic of the allergic response, while Hyde and Campbell[104] have repeated the statement in respect of both herpes and vaccinia injected intracerebrally. If these observations be confirmed, we must conclude that, taken alone, the recognition of allergic components in a composite histopathologic picture is a very insecure basis for regarding allergy as the etiologic factor of the morbid process. While, therefore, we fully agree with Ferraro on the undesirability of creating too easily new disease entities on the basis of possibly insignificant clinical or histologic deviations from a standard, we would equally guard against attempts to create a false unity among diseases of which most writers agree that the etiology is frankly not proven.

In any description which seeks to identify the lesions found in a spontaneous disease of man with a purely experimental condition produced in a laboratory animal it is always possible to minimize discrepancies between the two as resulting from differences in the response of various species to one and the same deleterious agency. In the realm of the demyelinating diseases we can sometimes make a direct comparison of two maladies of known and dissimilar causation within a single species. Cases in point are the encephalomyelitis in the dog given injections of brain with adjuvants and that following distemper in the same animal. A careful comparison between the *earliest* lesions in the two cases would go far toward defining the role of allergy in the latter. As stated previously, in our own distemper material the earliest changes following intracerebral (combined with intramuscular) inoculation of virus were unequivocally those of a direct attack by the virus on certain areas of the white matter, and it was only sometimes in cases of encephalitis arising in the field some weeks after the first systemic activity of the virus (antigen) that appearances which could possibly be accepted as hyperergic were encountered. Again, in the simian disease which has passed under many names including that of Schilder's disease in the monkey, demyelination may occur without any evidence of allergic inflammation. In the only cases we ourselves have examined[105] the lesions were wholly different from those pictured by others in the disease in monkeys evoked by injections of brain and, in fact, were wholly devoid of an inflammatory element. So also in the monkey poisoned with potassium cyanide, under certain conditions of dosage[72] there evolve lesions which fulfill King and Meehan's requirements for a demyelinating disease—"one in which the disease process attacks primarily and essentially the white matter of the brain."[100] In most parts of the white matter of these (chronic) cases there was no trace of allergic or other inflammation.

We conclude that, surveying the whole field of naturally occurring demyelinating diseases of man and animals, it seems quite inconceivable that there can be a common basis for all. Irrespective of whether or not it throws direct light on the pathogenesis of these naturally occurring diseases, the experimental evidence points to the many ways in which demyelination may be produced; in fact demyelination is merely the response of the white matter to noxious stimuli of a certain intensity. Still more does it point to the need for further experimental work, along several different lines, before a complete insight is obtained into the pathogenesis of this puzzling group of diseases.

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Epidemiologic Characteristics of Multiple Sclerosis

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OVER the past one hundred years thousands of clinical and laboratory reports describing the pathology and symptomatology of multiple sclerosis have been published. Numerous hypotheses have been advanced to explain its cause. Yet, today it is still uncertain whether multiple sclerosis is a degenerative, metabolic, vascular or infectious disease or whether it is a clinical syndrome due to a variety of causes. Even the nature of the pathologic lesion is in dispute, there being adherents to the concept that demyelination is associated with primary inflammatory processes, primary vascular thrombosis, or primarily degenerative changes.[1–4]

Central nervous system tissue can react to a variety of injurious agents in only a limited number of ways; one of these is the production of disseminated demyelinating lesions. It is possible that several agents (endogenous or exogenous) may be capable of producing such lesions. Numerous etiologic agents have been implicated in the disease[4] but none has been proved to be the cause in any series of cases.[3] The fact remains that the etiologic factor or factors of multiple sclerosis are unknown, and the "disease" that is being diagnosed as multiple sclerosis may actually be a clinical syndrome.

One approach to etiologic analysis is to ascertain whether any peculiarities of distribution among different population groups might suggest the operation of a specific factor. In the past such studies have paid particular attention to age and race selection and to geographic distribution. The opinion has frequently been advanced, and is now held by many physicians, that multiple sclerosis occurs principally in young white adults, that it is more common in cold than in warm climates and that its prevalence increases in areas farther from the equator. There is disagreement over the significance of genetic predisposition, the effect of infections or pregnancy on the inception or course of the disease, whether either sex is more predisposed to the disease and whether the frequency of the disease has been increasing. Some of the above mentioned items which are of particular interest to the epidemiologists will be reviewed and their implications as to possible etiology will be discussed.

The Problem of Accurate Diagnosis. The enumeration of cases and the development of rates and ratios for comparison are essential before anything can be said about the relative frequency of the disease. To count cases, diagnoses must first be made. The question arises as to how reliable the diagnosis of multiple sclerosis is. In the absence of a pathognomonic clinical finding or specific laboratory test, the only absolute method of diagnosis is by pathologic examination in fatal cases. Typical clinical cases are diagnosed with little difficulty by neurologists but the less characteristic forms are frequently diagnosed only after the exclusion of other neurological disease that may produce signs and symptoms of disseminated lesions of the central nervous system.

Some idea of the difficulty of the diagnosis is shown in a report on the clinical-pathological statements of causes of death based on data from fifteen New York and New Jersey metropolitan hospitals during the period 1930 to 1939.[5] In this study, covering about 25,000 deaths for which clinical and autopsy results were available, a clinical diagnosis of disseminated sclerosis had been made for thirty-three deaths. Of these, autopsy revealed ten as due to other conditions. On the other hand, eleven cases not diagnosed clinically as multiple sclerosis were so classified at autopsy. Thus

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about one-third of the clinical diagnoses of multiple sclerosis were in error and about one-third of the autopsy-proved cases had not been recognized clinically. Because autopsy is often a selective procedure for the difficult clinical cases and because of the small number of deaths in this study, the implication of error in these findings cannot be applied more widely. The extent of the diagnostic error in any series of cases will undoubtedly vary with different levels and conditions of medical care, the availability of neurologic consulting services, the concept of multiple sclerosis which the examining neurologist has and similar factors. It is possible that the frequency of the diagnostic error for multiple sclerosis may be greater in clinical studies or in field surveys which seek to enumerate not only advanced and fatal cases but also early cases which are presumably more difficult to diagnose.

Frequency of the Disease. Multiple sclerosis when first described clinically was considered a medical curiosity. Today, with the recognition of the variety of clinical forms that the syndrome may take, it is considered to be "one of the most common organic diseases of the central nervous system in many parts of the world."[6]

Annual variations: The question arises as to whether multiple sclerosis is becoming more frequent. Steiner[7] thought that there was an "increasing incidence of the disease in various countries" but believed it was "apparently due to more widespread knowledge of its clinical appearance." MacLean[8] found that the average annual incidence of multiple sclerosis in Rochester, Minnesota, from 1912 to 1926 was only slightly less than that from 1927 to 1947. Sällström[9] points out that for the ten-year period 1925 to 1934 he found no evidence of any increase or decrease in incidence in Sweden. The average annual incidence rates from 1939 to 1948 were also stable in three cities in which surveys were made in the United States and Canada (Boston, New Orleans and Winnipeg).[10] Limburg,[11] in 1947, found that the number of new cases diagnosed annually in the New York metropolitan area in the years 1936 to 1946 was stable. Prior to 1937 the number of cases diagnosed diminished year by year. This trailing off of cases by time of onset or date of first diagnosis has been interpreted by some clinicians as indicating an increasing incidence of the disease. But the decreasing number with time is expected, since the earlier the time of onset is in relation to the date of the study the more likely it will be that earlier cases will be excluded because of death, migration, recovery or change of diagnosis. In Limburg's review of the multiple sclerosis mortality statistics in the United States and Canada from 1939 to 1946,[12] the rates per 100,000 population increased from 0.9 in 1939 to 1.1 in 1945 but dropped to 1.0 in 1946. Limburg also reported that the death rates per 100,000 in British Columbia increased steadily from 0.9 in 1940 to 5.6 in 1944; but this writer found that the "increase" was due to an error of classification in the British Columbia death certificates whereby cases of cerebral arteriosclerosis, which had been included in the multiple sclerosis category during that period, accounted for the apparent rising death rate.[13]

There appears to be little evidence that the frequency of multiple sclerosis has been increasing in any given area over the short period during which any reliable data are available.

Seasonal variations: Onsets and exacerbations seem to occur at any time of the year. Limburg[12] was unable to demonstrate seasonal variations in the estimated month of onset, estimated month of recurrence or the reported month of death for several samples of morbidity and mortality data. Ziegler[14] states that "the disease may make its appearance at any season of the year, but I have felt that the onset and recurrences are more frequent in spring and early summer." No data are given to support this statement.

Geographic Distribution and Racial Selection. The geographic distribution of multiple sclerosis has been under investigation for several decades. Prior to 1948 published reports on this subject were generally based on personal observations, by surveys in limited geographic areas or by comparisons of proportional multiple sclerosis admission rates to hospitals in different localities. Out of such observations came the impression that the disease was rare in Africa, the Orient and South America, and that it was more common in the countries of Europe and North America which were distant from the equator.

A recent review of literature on this subject by the writer[13] concludes that, up to 1948, there had not been "valid evidence of a variation in geographic distribution of the disease." Although a large variety of studies had been conducted, "in the analysis of the results little consideration has been given to the effect of time on the diagnosis of multiple sclerosis, to

differences in the methodology employed, or to the comparability of medical facilities available in different communities."

In 1948 Limburg reported on the geographic distribution of deaths classified as multiple sclerosis.[12] Death rates were found to be higher in countries more distant from the equator; but the variations in the mortality statistics may have been more an indication of the lack of accurate death certification or classification systems in the countries nearer the equator than an indication of a real difference in frequency.

One comparison out of Limburg's study especially worth while, however, is that of the death rates in the United States and Canada. In these countries, language, medical practice, medical certification at time of death and the classification system used in coding deaths are similar. Limburg found that mortality rates in Canada and the Northern States were higher than in the Southern States. Following Limburg's study, Kurland and Moriyama[15] described errors in the certification system of multiple sclerosis deaths whereby deaths due to cerebral arteriosclerosis had been included in the multiple sclerosis category. In spite of corrections for this error and additional corrections for age and color differences in the populations of the regions of the United States and Canada, multiple sclerosis death rates were still higher in Canada and the northern regions of the United States than in the South.[13] It was also found in that study that the death rates for the white and non-whites of the southern United States did not differ from each other by a statistically significant amount.

Kolb[16] reported that the multiple sclerosis admissions to three large hospitals in Baltimore from 1929 to 1940 showed no selection for color or country of birth and Chiavacci et al. reported that there was no predilection for any racial or national group in New York City.[17] Cases in New York were found among all groups including Asiatics residing in the city. As the data in these studies were collected from a limited number of sources, the total frequency of multiple sclerosis reported for Baltimore or New York cannot be compared to the frequency reported in other studies.

Surveys of the frequency of multiple sclerosis were conducted by the writer in New Orleans, Winnipeg and Boston in 1949 and 1950. Reports of diagnosed cases were obtained from all the available medical facilities in each community. Analysis of the survey methods employed in the three cities indicates that the studies were equally thorough. The results can be summarized as follows: The prevalence ratios in Boston and Winnipeg as of January 1, 1949, were almost identical and each was three and one-half times the prevalence ratio for New Orleans. Similarly, the average annual incidence rates and the average annual mortality rates for the ten years from 1939 to 1948 were three times higher in Boston and Winnipeg than in New Orleans. There was no statistically significant difference between the white and non-white rates in New Orleans or between the white and non-white rates in Boston. In addition, it appeared that in each city the rates for native and foreign born populations were similar.

In New Orleans there was not a single autopsy-confirmed case for the ten-year period of the study. In Boston there were twenty autopsy-confirmed cases and in Winnipeg, a city with half the population of New Orleans, six cases had been confirmed by autopsy.

The prevalence ratios in Boston and Winnipeg were similar to those found for Kingston, Ontario and Rochester, Minnesota, by other investigators[8,18] who also conducted surveys of all medical facilities in their communities. The prevalence ratio in the northern communities is about 40 to 55 per 100,000 population while that for New Orleans is about 12 per 100,000 population. As yet, multiple sclerosis prevalence has not been satisfactorily determined for any community situated between the northern cities studied and New Orleans.

Urban-Rural Comparison. Earlier reports (Allison[19]) and more recently that of Steiner[20] support the viewpoint that multiple sclerosis is more often a disease of the rural dweller and agricultural worker than of the city dweller. Others have found that the distribution of cases closely followed that of the general population. Sällström reported equal rates in urban and rural areas for Sweden for 1925 to 1934. The study of Bing and Reese[21] in Switzerland reveals no difference in urban-rural rates that cannot easily be explained as a chance happening. The prevalence ratios in two small towns and two large cities of the northern United States and of Canada (Kingston, Rochester, Winnipeg and Boston) indicate that the ratios in these communities do not differ from one another by statistically significant amounts. Limburg found no difference in the multiple sclerosis death rates among rural and

urban dwellers in Holland or Scotland. Death rates in New Orleans, Boston and Winnipeg were similar to those reported for their respective states and province.[13]

On the basis of more recent information, it would appear that there is little evidence to indicate a predominance of multiple sclerosis in either urban or rural areas.

Focalization of Cases. There is no evidence to indicate that there has ever been an "epidemic" of multiple sclerosis. There have been a few reports of several cases occurring in the same area. By chance alone, one might expect occasional concentration of cases even in a disease which might be distributed randomly.

Campbell, Herdan, Tatlow and Whittle,[22] in their report, "Lead in Relation to Multiple Sclerosis," describe the occurrence of six cases living within 500 yards of one another in a small village in Berkshire County, England. This instance came to light in the course of a postal survey of multiple sclerosis in four large English counties. The cases occurred over a period of years; the exact dates are not given.

Lead was carefully studied and reported as a possible etiologic factor, as the lead content of the soil in the small village was found to be high. However, no such focalization of the cases nor any unduly high prevalence was reported for other areas in England showing equally high concentration of lead in soil. The authors also found that the lead content in the teeth of multiple sclerosis patients was greater than that of normal controls from the same geographic area.[22,23] It has been hypothesized that multiple sclerosis symptoms may be due to damage brought on by release of lead from bones when calcium is mobilized in acidotic conditions of infection, pregnancy or trauma in susceptible persons. If lead is involved in the etiology of multiple sclerosis, there must be additional factors which are not understood. The geographic distribution of lead is almost world-wide. Mexico and Spain are both large producers of lead, yet no unusual prevalence of multiple sclerosis has attracted attention to these countries. Furthermore, there appears to be no occupational selection in multiple sclerosis. If exacerbations could be brought on by lead released to the blood stream from bone during calcium mobilization, experimentally induced acidotic conditions which are said to mobilize calcium should theoretically cause exacerbations if lead is involved. Such a hypothesis has not yet been tested although ACTH, which is said to increase calcium mobilization from bone, also has no detrimental effect on the course of multiple sclerosis.[23a]

Campbell, Daniel, Porter, Russell, Smith and Innes[24] have described the occurrence of a neurologic condition resembling multiple sclerosis in four persons doing research work on swayback, a demyelinating disease of lambs. This, too, may have been a coincidence but the occurrence of this outbreak of human disease in relation to a demyelinating disease in another animal would appear to warrant further study. Campbell et al.[22] state that there is a possible association of lead toxicity and swayback, and that areas in England with higher swayback incidence also have greater multiple sclerosis frequency. However, the highest multiple sclerosis prevalence ratios reported anywhere in the literature based on extensive surveys are those reported in the northern United States and in Canada,[8,10,18] and in these areas swayback has not occurred.[25] As copper supplements in the diet of the pregnant ewe have been found to prevent swayback, copper metabolism in multiple sclerosis cases has been studied. No difference in blood copper or urinary copper excretion has been found between patients and normal controls.[26,27]

The writer is not acquainted with any unusual massing of cases within a large region or city of the United States or Canada. In three cities (Boston, Winnipeg and New Orleans) in which cases were collected, the distribution within the city appeared to be of a random nature. Two small communities in the United States (one, Ridgefield Park, New Jersey, and the other, Rock Falls, Wisconsin) were reported to have an unusually high number of cases but on investigation by the writer the number was found to be about as expected for those parts of the country.

Occupation. Brain[28] reviewed the literature available prior to 1930 on this subject and reported "there is no satisfactory statistical evidence of any occupational incidence of the disease." More recently this matter was again considered[9,12,19,20] and these reports have been analyzed by this writer. The conclusion reached by Brain remains unaltered for it appears that persons in almost any type of occupation and even young adults, before employment, may

be affected. The number in any occupational group affected seems to be proportional to the local number of persons in that occupation.

Age at Onset. The age at onset has been reported in numerous publications.[6] About two-thirds of the cases are reported to have their onset between ages fifteen to thirty-five. Frequency distribution curves by age of onset usually rise sharply from zero, below ages twelve to fourteen, to a peak at about age twenty-five, drop away sharply between ages twenty-five to thirty-four, then gradually taper off to zero at about age fifty. The median age of onset is about twenty-six years, the mean about twenty-eight years. According to Wechsler, Müller and others,[14,29,37] multiple sclerosis rarely occurs prior to age ten or after age fifty. In most studies[6,9,12] there is no appreciable difference in age of onset by sex. The age of onset as reported for different countries and for different sections in North America[6,8,9,10,16,18] do not differ appreciably.

The limitation of time of onset to the period between puberty and the climacteric might suggest the possibility that etiology may be related to some hormonal dysfunction. As yet there is no evidence to support such an hypothesis.

Age at onset must be known if duration of illness and the influence of therapy on the course of the disease are to be studied. But what is generally referred to as onset of disease is actually onset of first recognized symptoms. The disease process if mild or if in a silent area of the central nervous system will antedate the recognized symptoms.

The accuracy of statements as to age at onset depends on the acuteness of first symptoms, the patient's recollection of the episode and the physician's accuracy in taking and recording the history. It seems that the further advanced the case is when the history is recorded the more likely it is that the time of a later exacerbation will be recorded as onset. This would seem to be the most plausible explanation for the discrepancy in studies of duration by the retrospective and by the follow-up or life table methods.[31]

It has been found that retrospective studies of duration of disease in those who have died show a considerably shorter average duration than do studies using the life table method or studies in which a group of living patients have been followed for many years. By the retrospective method duration of diseases in patients studied averaged about ten years;[9,16,30] by the life table method life expectancy was found to be about twenty to twenty-five years.[31] Allison[32] in a follow-up of patients first seen about 1930 found the average duration of life after onset to be slightly over twenty-two years.

Sex. There is no consistency in sex distribution of diagnosed cases in published reports. Müller discussed this point in his monograph. In most of the published reports the proportion of males to females is presented without any attempt to relate this to the total hospital or clinic populations from which the cases are drawn. As some hospitals or clinics have a different proportion of male and female patients, the number of multiple sclerosis cases by sex alone is not very helpful.

There are several studies in which the total case load was related to the total population from which the cases were drawn. In Sällström's collection of the hospitalized cases in Sweden from 1925 to 1934 there appeared to be no difference in frequency by sex for the country. The proportions of male or female cases to total hospital admissions by sex were also equal. In Bing and Reese's study based on reports from private physicians as well as hospitals in Switzerland, 60 per cent of the 891 cases were among women; 54 per cent of the population were females. In another report by this writer[10] total multiple sclerosis mortality rates in the United States and Canada were found to be equal for the two sexes. Mortality rates were equal for the two sexes in New Orleans, Boston and Winnipeg, but morbidity in the three cities, based on reports collected from hospitals, clinics and physicians, revealed a ratio of about three female cases to two male cases in each city. It was found, however, that the comparison of the cases restricted to those who had died or had been hospitalized revealed little difference by sex. The preponderance of female cases was due to a higher proportion of living female cases reported by physicians. It was suggested from this that more cases of hysteria among the women may have been erroneously diagnosed as multiple sclerosis, or there were more early cases of multiple sclerosis among the women. If women seek medical care earlier in the course of a disorder such as multiple sclerosis than men do, a higher proportion of earlier cases among females might be located in community-wide surveys of all sources of medical information, even though there might be no real difference in sex distribution of cases. If the hospi-

talized cases are the more severe ones, there would appear to be no difference in frequency of the advanced cases by sex.

Familial Occurrence. The occurrence of multiple cases in one family has attracted attention for many years and a number of supposed instances have been reported. Since the presence of familial aggregation of cases might point to some hereditary or environmental causative factor, it seems worth while to review the evidence in this field.

There are several factors that may influence statistics in this type of study that should be considered. First, it is recognized that multiple sclerosis may often be difficult to differentiate clinically from recognized hereditary degenerative diseases, such as Friedreich's ataxia and hereditary cerebellar ataxia. On the other hand, for decades multiple sclerosis has been considered as a disease which does not occur in family groups and it may be, as Mackay[33] suggests, that "the skilled neurologist may exclude the apparently justified diagnosis of multiple sclerosis upon the discovery of more than one case in a family because he has always considered multiple sclerosis to be non-familial."

There is the additional problem of defining the extent of the "family." In determining whether the number of "familial" cases in a series is greater than would be expected by chance, it is necessary to know the frequency of the disease in the population at large, and it is necessary to know the number of family *members* "at risk." If sufficiently distant relatives are included in the family, the family population at risk would be considerable and a number of familial cases in any large series might be expected to occur by chance. Even where the family is defined so as to include only siblings and parents or spouse and children, the total population of family members rather than the number of families must be taken into consideration in developing rates.

Most reports dealing with this subject supply the number of "familial cases" with no attempt to present any rates or ratios. Sällström[9] and Mackay[33] mentioned a total of sixteen cases in one parent and one or occasionally two or three offspring reported in the literature from 1896 to 1948. Pratt et al.[34] in 1951 added four additional instances of disease in a parent and offspring. Most of these are not autopsy confirmed and several are poorly described clinically.

Mackay in his comprehensive review of the literature found a total of eighty-four family groups with an aggregate of 177 persons among whom "adequately described and acceptable instances of multiple sclerosis" were found. To this might be added thirty-eight additional "familial cases" acceptable to Pratt et al. and two more reported by Kolb[16] not included by either Mackay or Pratt.

It is difficult to evaluate the importance of these instances among the tens of thousands of cases that have occurred over this period. As "family" will at times include cousins, aunts, uncles, nieces and nephews as well as siblings and parents, the total population base in whom such family cases occur is impossible to determine.

Some authors have computed the ratio of the number of "familial cases" to the total number of cases in a consecutive series. Pratt, Compston and McAlpine in their review of the literature found that this ratio varied from 0.0 per cent in a series of 300 cases reported by Barré to 5.6 per cent (8 of 142 cases) reported by McAlpine. The average ratio in this collection of reports on over 4,500 cases was 1.8 per cent. Sällström[9] reported that in his own experience as well as that of Bing and Reese[21] and Curtius[35] "familial cases" made up about 1.5 per cent of the total cases collected. Sällaström indicated that since the total occurrence in the Swedish population was only about 0.02 per cent, the occurrence of cases in 1.5 per cent of the *families* indicates "a frequency about 80 times greater within the families of patients than within the total population." This conclusion is not correct for Sällström has compared frequency among individuals (cases per unit of population) with cases among groups of undetermined size (families).

In only one report with which the writer is acquainted[34] has any attempt been made to compare the number of observed cases in a defined family size with the number expected on the basis of the prevalence in the total population. Among the 1,003 living parents and siblings of 310 multiple sclerosis patients studied there were eight who were said to have multiple sclerosis. This is higher than expected by chance (0.5 cases "expected" if total prevalence ratio of 50 per 100,000 population for England is applied to the 1,003 family members). Even if it had been possible to be sure that a few diagnoses of an hereditary degenerative disorder were not included in this series, at most it can be said that in only a small fraction

of all cases would any "familial" factor seem to be operating.

Curtius[35] considered the presence of any nervous disease in the family as an indication of a "constitutional predisposition." He found a greater frequency of psychiatric, neurologic and developmental defects among blood relations of a group of multiple sclerosis patients than among the blood relations of a group of patients with fractures. He suggested that the individual with multiple sclerosis comes from stock which is predisposed to develop disorders of the nervous system. One objection to the acceptance of differences obtained in this manner is the likelihood that a patient with multiple sclerosis or the members of his family may be more aware of neurologic disease in the family than otherwise.

The reports on cases occurring in a spouse are so rare that the operation of chance seems to be a most plausible explanation when they do occur. Steiner[20] mentions the only observations of conjugal cases prior to 1938, one observed by a colleague and another by himself. His statement that such occurrences argue for contagion completely overlooks the possibility of a coincidental circumstance.

In the light of this information on familial aggregation of cases, it might be best to define congenital and hereditary disease and see how well the evidence points to such an occurrence.

In order that a disease be considered congenital one must prove that it was transmitted to the germ plasm, embryo or fetus in *utero*, and that it was present in the child at birth although it need not to have manifested itself immediately afterward. The only report with which the writer is acquainted in which the question of congenital multiple sclerosis is considered concerns a mother and her eight year old son who were said to have died of multiple sclerosis.[36] However, Pratt et al. who later reviewed the cases did not believe the diagnosis of multiple sclerosis was correct because sclerotic plaques were not found in the brain stem of either case. There appears to be no evidence in support of a congenital form of multiple sclerosis.

To speak of a hereditary disease one must show that it existed in some of the ascendants and collaterals, that it manifested itself in the descendants and that it affected the various persons with a fair degree of consistency. There are so few confirmed cases of multiple sclerosis in families which would meet these criteria that most observers avoid any reference to multiple sclerosis as a hereditary disease. As familial aggregation of cases appears to be the exception rather than the rule, neither heredity nor the possibility of contagion would seem to play an important role in the etiology of multiple sclerosis.

Pregnancy. Childbearing (pregnancy, delivery and puerperium) has frequently been considered as a factor in the onset or exacerbation of multiple sclerosis. As Müller[6] notes in his monograph this has never been proved. Von Hoesslin[38] noted that pregnancy and parturition were related to onset or exacerbation in about 6 per cent of the female cases. Kolb reported it in 10 per cent of his cases, and most authors quoted by Müller note the relationship in about 10 per cent of their cases.

Tillman[39] reported that of 278 female cases in the records of the Neurological Institute in New York, ninety-nine patients were single, forty-seven patients, while married had never been pregnant, forty-seven patients had the onset of disease prior to pregnancy, in six patients the first symptoms began in pregnancy and in seventy-nine patients the first symptoms followed (indefinite time) pregnancy. It is obvious that onset may develop before, during or after pregnancy. The question arises as to whether onset or relapse when it does occur is coincidental or related to childbearing.

If we were to accept for onset or relapse associated with childbearing a figure of 10 per cent of the female cases, we would have to know how this compared with what might be expected by chance alone. The age distribution at onset corresponds to the age period of childbearing (approximately fifteen to forty-five years of age) or over a thirty-year span. If the average woman has three pregnancies, she spends about thirty-six months or 10 per cent of the time in this period in a pregnant or postpartum state (the latter for convenience taken as three months).* Thus, by chance alone, the period of childbearing and multiple sclerosis onset or exacerbation might occur simultaneously to the extent reported.

It will be argued that this simplification fails to consider the fact that physicians often advise multiple sclerosis patients against pregnancy

* Weinstein et al[40] estimated from rates of living and stillbirths that approximately 7 per cent of women in age groups twenty to forty years would be pregnant at any given time. If the postpartum period of three months and the time spent in pregnancy that end in abortions are included, a figure of 10 per cent appears reasonable.

and that this would lower the pregnancy rate among the multiple sclerotics. For a more precise comparison of the relationship of multiple sclerosis to childbearing the reader is referred to the special study of this problem by Müller[6] in which the rates of onset or exacerbation in non-pregnant women are compared to those of pregnant women. In that careful statistical analysis Müller found that childbirth did not increase the risk of onset or exacerbation.

Spectrum of Disease: Remissions and Exacerbations. For most diseases of man there is variability in the severity of clinical cases. Some patients may have an acute and fulminating attack, others may have severe disability, others a mild disorder, still others only an abortive case or a subclinical case, i.e., one detected by laboratory methods in the absence of signs or symptoms. The collection of such cases makes up the so-called "spectrum of disease," i.e., both the clinically identifiable cases and those detected by laboratory methods only. The proportion of the severe to the mild cases or the clinical to the subclinical cases varies with each disease.

Multiple sclerosis is not recognized over the entire range of such a spectrum, and it is suggested here that the manifestations of the milder forms may never be identified. Multiple sclerosis is known to occur in an acute and rapidly progressive form as well as in slowly progressive and remittent forms.

Remissions are said to occur in almost half the recognized cases.[3] Most are of short duration but prolonged remissions which occasionally occur are usually recognized as remissions only when an exacerbation follows. If the remission appears to be complete and permanent, the diagnosis of multiple sclerosis will rarely be retained.

Perhaps there is also a mild or "abortive" form of multiple sclerosis which occurs as a single attack and clears completely. Such cases probably receive vague diagnoses for there may be no recurrence of disability or the patient may die of another cause before there is a recurrence. Retrobulbar neuritis, for example, is one symptom complex that is often associated with multiple sclerosis. Many cases improve and show no progression or recurrence of neurologic dysfunction while in others typical multiple sclerosis occurs. Were the cases which cleared a part of the same disease process as those which progressed? The diagnosis of multiple sclerosis in cases in New Orleans and Winnipeg was not established by physicians reporting the cases until an average of about five years after onset of symptoms. Such cases were usually diagnosed only because of progression or recurrence of symptoms. It is suggested that other cases with similar onsets but no recurrence or progression may be unrecognized forms of the same disease process.

In the absence of a specific laboratory test a subclinical form of multiple sclerosis cannot be identified.

Remissions and exacerbations are somewhat characteristic of this neurologic disorder. It is not clear what they represent from the standpoint of the nature of the disease. Some questions that might arise, although answers are not provided, are these: Are remissions the result of the destruction or removal of an external causative agent or is there some physiologic change in the host that establishes an equilibrium between host and agent? Are exacerbations due to repeated invasions by exogenous agents or do they represent breakdowns in the host's protective mechanism to some agent, perhaps permanently fixed, in the body of the host?

COMMENTS AND SUMMARY

The frequency of multiple sclerosis in North America varies with latitude but not with season or by year. Within any region it appears to be randomly distributed among all races, nationalities, social levels and occupational groups. It occurs in both sexes and appears to be selective only in age of onset, since adults, mainly young adults, are affected. Heredity, contagion and pregnancy play no role in its selectivity. The reported difference in frequency with latitude would seem to be due to a variation in the amount of exposure to some external causative factor or factors rather than to a difference in the inherent susceptibility of any population. However, as multiple sclerosis may be a clinical syndrome the difference in frequency with latitude may be due to the absence, among the indigenous cases in the South, of a specific causative factor which my be responsible for the majority of the northern cases.

Concepts of etiology are discussed in detail in the recent reviews by Reese[4] and by Schumacher[3] and in the present discussion only those items on frequency and distribution which relate to some of the more recent hypotheses of etiology are considered.

As the incidence of multiple sclerosis and

climatic conditions both vary with latitude, cold has been suggested as a causative factor. Chilling which may alter coagulability of blood is suggested as a cause of venular thrombosis in the nervous system. Thrombosis has been suspected as one pathogenic mechanism[3] but remains unconfirmed. Dietary deficiencies[3,41] and excesses that may vary in different regions[42,43] have also been investigated but with little success to date.

The similarity of the geographic distribution of multiple sclerosis to that of rheumatic fever has been noted.[44] Disabling acute respiratory disease, at least as manifested in the Armed Forces in the United States during World War II,[45] also shows a higher frequency in the northern areas than in the South. The cause of rheumatic fever is unknown but a hypersensitive reaction to streptococci (and perhaps a virus) is suspected. It has been suggested[46] that multiple sclerosis may also be a manifestation of an allergic hypersensitivity. However, the sequence of events which could "initiate such an allergic reaction in human beings (liberation from the central nervous system of the tissue antigens stimulating antibody formation, which in turn react with the original tissue) . . . are as yet completely unknown."[46] Nevertheless, it is of interest that Störtebecker[47] has reported evidence of bacterial infection in patients "with multiple sclerosis and with various neurological manifestations that as a rule are the first symptoms of multiple sclerosis." Regression of nervous symptoms was said to coincide with an apparent subsidence of the infection as determined by serologic determinations of antistreptolysin, antistaphylolysin, coli-agglutination titers, sedimentation rates and leukocyte counts. (However, Störtebecker's interpretation of what constitutes significant differences between the results for the cases and for normals seems rather loose.) If a combined infectious and allergic mechanism operated, one might expect to find some precipitating infection preceding the first bout of the disease. Prodromal symptoms or constitutional signs at onset might also be expected but they either occur infrequently or are not recognized if they do occur. One might also expect that persons in whom such a hypersensitive response might occur would also have other indications of allergic tendencies, but this does not appear to be so.[3] The explanation of cause on an infectious and allergic basis must remain in the realm of speculation until some of the other intensive laboratory and clinical research on the allergic mechanism now under way enlightens us more.

The variation of frequency with latitude has led to the recommendation[48] that patients migrate to warm dry climates. The effect of such a change of residence has not been carefully evaluated as few patients have been followed to determine how well they responded. Of course, a test of the response to such therapy is a most difficult one to evaluate because even without change of residence (and with no treatment for that matter) some patients spontaneously have remissions. Furthermore, even if a change of climate were a "specific" form of therapy it would have no effect on scarred lesions.

In an attempt to clarify the effect of climate on outcome of disease, determinations of life expectancy of patients in New Orleans, Winnipeg and Boston are being carried out. Preliminary studies reveal that in all three areas the life expectancy after onset is about twenty to twenty-five years. There is no statistically significant difference between the mortality rates among patients in the three cities. If the data on the cases and deaths in the cities[10] were collected with equal accuracy and if multiple sclerosis is a specific disease entity, it would appear that once the disease begins, its course is not influenced by place of residence. The similarity of life expectancy of the patients in the three communities would also suggest that if greater prevalence of an external causative factor is responsible for the higher frequency in the northern communities than in New Orleans, an endogenous mechanism rather than repeated exposure to the external causative factor is responsible for exacerbations which shorten life.

There are no formal conclusions regarding etiology to be derived from these epidemiologic data. But the hypotheses that may be developed or tested to explain cause will have to account for the differences and similarities in frequency and distribution which have been here noted.

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Trends in Etiologic Researches of Multiple Sclerosis

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RESEARCHES in multiple sclerosis today continue to be focussed on the complex biochemical disturbances, primarily in myelin sheath metabolism and supplementary extrinsic factors such as toxic-infective or other excitating causation. Possible etiologies have been discussed abundantly in the literature, supported from time to time by more than 200 mostly unsuccessful treatment schedules. The latest references to the total problem of multiple sclerosis have been reported by the American Association for Research in Nervous and Mental Disease in 1951[1] and by G. Schaltenbrand, Germany.[2] The imperative question: What really is the etiology of multiple sclerosis? cannot be answered, however. From many reports from various countries the conclusion is reached that it is most probably not a transmissible infectious agent, that it is not a deficiency of nutrients, but that it may be a myelin dyscrasia specific for human beings, endogenously developed by mobilized enzymes with myelinolytic properties. The search for the cause of abnormal pre-lipids or phospholipids (myelin disintegrative products?) and of metachromatic substances is a problem for histochemists. The analysis of myelin[3] and of myeloclasis calls for the special technical skills of enzyme institutes, and the investigations of the oligodendroglia in reference to the nutrition and disintegration of myelin[4] is a cytoplasmic research problem for the neuropathologist. Statistical surveys of multiple sclerosis render little if any support for an infectious theory for the formation of disseminated islands of demyelination and of gliosis with rather sharply defined contours. The vascular origin of multiple sclerosis is suggested by plaques related to central venules in the subependymal regions but in the majority of cases a relationship between vascular alterations and foci of demyelination cannot be established. Putnam's thrombosis theory cannot be rejected completely in the pathology of acute or very early multiple sclerosis, but his explanation of venous thromboses based upon a faulty prothrombin or clotting mechanisms has been disproved as a possible determining factor. I concur with Lumsden,[4] who states: "The problem of the causation of multiple sclerosis has been narrowed to a choice of two views: either (1), if the real cause is a specific transmissible agent it must be a virus or a chemical substance not yet even listed amongst the known pathogenic agents, and one with some extremely uncommon properties; or (2) alternatively, the disease may be only a specific form of reaction on the part of the nervous system peculiar to certain individuals and, within limits, independent of its immediate precipitating cause." What basic knowledge is on hand for such an assumption?

After reading and studying the voluminous literature offering a variety of etiologic theories the fact remains that multiple sclerosis is a uniquely human disease sui generis. Heredity, constitution, geographic distribution, climatic, soil and nutritional analyses have been evaluated without giving a clue to etiologic probabilities. Vaccination, serum or immunization "records," and the many infectious disorders "with a toxin circulating in the blood stream" and with consideration of a possible intermediary host transmissions have been investigated without conclusive results. The endogenous "glia" pathoclisis, the idiopathic myelin dyscrasia and the myelinolytic lipolytic ferment theories have been unjustly rejected, although all three offer greater potential avenues for investigation of a basic etiology of multiple sclerosis. Even though the infectious etiologic investigations on bacteria, spirochaetes and viruses have not yielded results, we must keep in reserve the possibility that endo- or ectotoxins of microorganisms (polysaccharides?) can and do influence the enzyme homeostasis and might liberate enzymes of toxic properties both to the

myelin and the glia. These in turn might precipitate the characteristic discontinuous, periaxial demyelination and secondarily the slow formation of eccentric sclerotic plaques. Miscellaneous factors, such as intoxications (with lead, manganese, cyanide), or trauma, "colds" and severe emotional stress may produce histotoxic anoxia mainly in the myelinated parenchyma; deficiency in trace elements such as cobalt (B_{12}) or copper may initiate vascular disturbances and impair glycogenesis in the central nervous system, which factors in turn affecting the enzyme system could liberate lipolytic or myelinoclastic toxins in multiple sclerosis. It is my belief that deductions from animal experimentations and demyelinating diseases in animals, although extremely valuable in our etiologic searches of multiple sclerosis, are not reliable and comparative, since the experimentally induced disseminated encephalomylitides are similar to but not identical with multiple sclerosis. The study of neuro-allergy and demyelination is complex, since the sensitizing neurotoxic factors as well as hyperergic (antigen-antibody) reactions in relation to multiple sclerosis have not been established. The allergic theory must be further studied, since fascinating similarities with distribution of multiple sclerosis plaques have been produced experimentally by injections of heterologous and homologous brain tissue with adjuvants.

Collier and Greenfield,[5] from their studies in the encephalitis periaxialis of Schilder and the leucodystrophies, deduced that the oligodendroglia was especially affected, and that the primary attack in demyelinating diseases was upon these cells that have to do with the nutrition of the myelin sheaths and the myelin metabolism. The role and the functional integrity of the oligodendroglia cells in multiple sclerosis is stressed by Lumsden[6] who demonstrated a loss of these cells about plaques of demyelination in the acute and in the chronic forms; and furthermore he attested that the oligodendrocytes disappear as abruptly as the alteration in the myelin sheaths begins. Lumsden's challenge that "the whole obscure problem of the demyelinating diseases may prove to be in the biology of the oligodendrocyte, the most numerous cell within the central nervous system," needs urgent study and verification. However, at once the question presents itself: What endogenous or exogenous factors alter the biology and cause regional malfunctions of the oligodendrocyte? Why then the intermittancy in the clinical course of multiple sclerosis?

CONCLUSIONS

The primary causation or nature of demyelination in multiple sclerosis is unknown. Intrinsic factors relate to (1) the biochemistry of the myelin protoplasma with its unusual protein to lipid ratio, (2) the functions of enzymes upon the myelin metabolism and catabolism, to which (3) we should add Lumsden's reference to the role of the oligodendroglia cells. The much discussed extrinsic factors all may precipitate at a given "traumatic time" disturbances more specifically in the myelin homeostasis, and thus may evolve the waxing and waning clinical symptomatology. The available non-specific therapeutic efforts have ameliorated the progress of multiple sclerosis only at times, without permitting any deduction as to etiology.

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Is Multiple Sclerosis Caused by a Virus?

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WITHIN the past eight years two papers,[1,2] have reported identification of a virus as a cause for multiple sclerosis. Although these results have not been confirmed by other investigators, the question still remains open whether this disease originates through the action of a pathogenic micro-organism. The concept of infection seems to have been first advanced by Pierre Marie in 1884 and reiterated at intervals since that time. Since no explanation of etiology has been found, infection and, more specifically, viral infection remains a possibility. This paper reviews available evidence for and against a virus hypothesis and discusses the need for further experimental studies.

From 1868, when Charcot formulated the classical description of this disease, until quite recently, multiple sclerosis was regarded as a medical rarity.[3] Because of this view perhaps little attention was given to the experimental search for a micro-organismal cause, even in the heyday of bacteriologic discovery. Today multiple sclerosis is known to be one of the commonest disabling structural disorders of the central nervous system.[4–7] However, we find that records of attempts to transmit the disease experimentally are not voluminous, but doubtless many trials have failed and were never published.

The virus hypothesis is only one of many possible causal ideas which have been promulgated to explain the origin of this disease. Such pathologic concepts as anoxia, lipolytic enzymes, vascular thrombosis, glial overgrowth, developmental factors and exogenous toxins have been recently reviewed.[8] However, while these try to elaborate the mechanism of pathologic processes, none offers factual explanation of cause. The relationship of lead intoxication to multiple sclerosis is unproven but may merit further study.[9] An iso-allergic mechanism has also been suggested because of the action of an unidentified agent in normal mammalian brain which can produce encephalomyelitis when injected into laboratory and domestic animals.[10–13] The spirochetal theory, first put forth by Buzzard forty years ago and still supported by Steiner, has never been confirmed in spite of modern advances in technics for isolation of bacteria.[14–25]

I. CLINICAL EVIDENCE

One argument against the infection hypothesis is that patients with multiple sclerosis do not show the constitutional signs and symptoms traditionally associated with bacterial and viral diseases, such as fever, leukocytosis, dehydration, general malaise and catarrh. However, several diseases of established micro-organismal origin also fail to show such effects throughout much of their course (e.g., lues, leprosy and certain phases of tuberculosis and brucellosis). Fever and other constitutional symptoms are also not unknown in multiple sclerosis.

It is also argued that the chronic nature of classical multiple sclerosis, with its remissions and relapses, does not suggest an infectious cause. However, we may point to such human and animal infectious diseases as tuberculosis and brucellosis which in some stages of pathogenesis are also chronic, and to the possibility that endogenous reinfections in these cause relapses. There is even evidence that an infectious agent may cause other long-drawn out nervous diseases according to observations on subacute sclerosing encephalitis or inclusion-body encephalitis;[26–29] no virus has yet been isolated for this disease but circumstantial evidence points to a viral cause.

Recent studies have confirmed earlier ob-

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servations that multiple sclerosis is least prevalent in regions nearest the equator.[6] Three to four times as many cases were found in selected cities of Canada and northern United States as in comparable cities of southern United States.[7] This difference is independent of racial differences in the populations and apparently points to an environmental factor. We realize that this environmental factor need not be an infectious agent; certain deficiencies or excesses in diet[30] or exposure to certain toxic substances may also be related to geography, as in pellagra, goiter and other diseases. But geographic distribution may also be related to the effect of climate or some other regional factor on an infectious agent, the host or the vector.

There is no proven case of human transmission of multiple sclerosis. Four cases were diagnosed among a small group of workers investigating swayback, a demyelinating disease of lambs,[31] but such an isolated instance cannot be weighed too heavily in the balance.

Multiple sclerosis is said to occur among members of the same family more frequently than would be expected by chance.[32,33] This finding might indicate some genetic predisposition rather than intrafamilial infection; but in these studies the erroneous diagnosis of a few cases of hereditary diseases, as cases of multiple sclerosis, also might account for the observation.

II. PATHOLOGIC EVIDENCE

Studies of morbid anatomy have long led investigators to suspect an infectious cause for multiple sclerosis.[34] In his magnificent treatise on the pathology and pathogenesis of disseminated sclerosis Dawson[35] emphasized the engima (persisting to this day) surrounding differentiation of the effects of inflammation from those of degeneration in the nervous system.[36,37] Contributing to this problem, according to King and Meehan,[38] has been the tendency to study the histologic details of myelin loss instead of tracing disease processes. In attempting to support certain etiologic concepts emphasis is laid by different observers on particular pathologic patterns.

The pathologic process involved in multiple sclerosis is accepted to be selective myelinoclasis, occurring in irregular, discontinuous patches in the central nervous system, with relative resistance of the neurones and axis cylinders to destruction. The total lesion, with its gliosis, progresses to the formation of sclerotic plaques. Description of the whole process was meticulously furnished by Dawson,[35] some gaps are filled by recent publications.[12,39]

Until recently no virus was known to produce demyelination nor had demyelination been found in neurotropic virus infections.[40,41] It is now known that some virus infections, in dogs at least, can cause demyelination as part of an infectious process.[38,42] It is believed that purely pathologic studies will make little contribution in the future toward elucidation of cause except by way of attack on fundamental problems of inflammation and of myelin.[12,43,44] This in turn would be intervolved with improvement of technics in histochemistry and biochemistry for studies on structure of myelin, and on the mechanism of the degradation of myelin in disease evoked by various agents. These are such complex, although basic, methods of attack as to be projects which might take decades to complete before there could be some practical application to multiple sclerosis. This should not be a deterrent to other approaches, for the goal in medical research, from the point of view of humanity, is that of control of disease by any measure, even without complete understanding of nature and cause.

III. PROBLEMS OF DISEASE CLASSIFICATION

Although Charcot's classical clinical description of multiple sclerosis stood for many years as the only basis of diagnosis, it is now recognized that many cases may be multiple sclerosis which do not show all of the clinical signs, the triad or any other complex. On the other hand, there is some question as to the relationship of the various demyelinating diseases to one another. As the virus encephalitides have been identified and classified as separate types of nervous diseases, so the tendency has been to group together all the demyelinating encephalopathies. Since this vogue was based upon visible pathology rather than on etiology, it is frankly provisional and, according to Russell Brain,[45] largely just a matter of "words." While some authorities believe that all of the demyelinating diseases are variants of a single entity (e.g., Ferraro[46]), there is no secure ground for believing that knowledge of what might cause such demyelinating diseases as post-vaccinal, post-infective, Devic's or Schilder's encephalitis, might necessarily throw light on the cause of multiple sclerosis.

There has been considerable interest in the

possible relationship of multiple sclerosis to acute disseminated encephalomyelitis. Marburg[47] originally contended that the differences were only quantitative, a view that has been upheld also by Dawson,[35] Turnbull,[48] Putnam,[49] Lumsden,[12] and many others. Van Bogaert[50] recently described five of nineteen patients with acute disseminated encephalomyelitis who developed classical multiple sclerosis; an acute form of multiple sclerosis has also been recognized.[51] R. Müller[52] believed that there was no essential differences between acute and chronic cases in either symptomatology or pathology beyond those residing in the speed with which new foci develop. He says "there is no safe foundation for assuming two different diseases exist." Since some cases of acute disseminated encephalomyelitis show clinical features of an infection, the relation from the point of view of viral cause between the two diseases deserves further study (c.f., the opinions of Wilson,[24] Brain[23] and McAlpine[4]).

IV. EXPERIMENTAL DEMYELINATION STUDIES AND ANIMAL PATHOLOGY

Neuropathologists generally agree that multiple sclerosis or any strict clinico-pathologic counterpart to human multiple sclerosis has never been observed in any species of the lower animal. Demyelination, however, does occur naturally in animals. It may be caused by a variety of agents, including trace element deficiencies, exogenous toxins, allergic reactions and viruses.[38,42,53] The canine demyelinating encephalitides appear to include several conditions, some caused by viruses or by mutants of a single virus. One of these distemper-like nervous disorders is acute and sometimes appears after constitutional signs of infection, while others are less well defined, perhaps chronic and may show remissions and relapses. The similarity of one form of canine encephalitis to human multiple sclerosis led Scherer[54] to call it *akute multiple Sklerose des Hundes*. Because demyelination is known to occur spontaneously in dogs, they might be the animal of choice in experimental work on multiple sclerosis.

Demyelination may be produced experimentally in laboratory animals by a wide range of chemical "poisons" (Hurst[55]). It has been found that the nature of the lesion produced might depend not only upon the agent but also upon the initial intensity of its action upon the white matter and the maturity of the white matter. Although much work has been done on experimental demyelination by toxic agents, such experiments have shed little light on the cause of multiple sclerosis.

A promising experimental approach has been work on the so-called iso-allergic encephalitis produced by injection of normal brain emulsion.[55–64] This work has renewed speculation on the possible role of induced hypersensitivity in causing multiple sclerosis. Pathologically, however, this condition does not resemble multiple sclerosis, although Wolf et al.[63] described a remitting course in a few monkeys and drew an analogy between the punched-out types of demyelinating lesions to human multiple sclerosis. According to Lumsden[12,64] the lesions in allergic encephalitis are more like those in post-vaccinal or post-exanthem encephalitis than in multiple sclerosis; he points out[12] that one feature of classical multiple sclerosis is lacking from the experimental lesions, that is, the progressive spreading demyelination, either in discrete plaques or in *Markschattenherde*.

V. EXPERIMENTAL TRANSMISSION OF MULTIPLE SCLEROSIS

Of the following eighteen reported studies eleven produced negative results and seven were interpreted by the investigators as positive.

Negative Results

1. Siemerling and Racke[65] (1911) in a discussion on pathology and pathogenesis refer to unsuccessful attempts to transmit infection by inoculation of CSF into two monkeys (Macacus rhesus), two rabbits and two guinea pigs. Siemerling[66] refers to this same work and mentions that in 1914 of two injected monkeys one showed lower limb weakness but recovered and was killed one year later at which time no sclerotic patches were found.

2. Simons[67] (1918) inoculated CSF (F, thirty-five years—lues excluded) which had been kept at 0°c. for ten days, into nine rabbits (one intracerebrally and one intradurally). Seven remained well; one animal which received 3 cc. in one sciatic region developed paralysis of hind legs, stopped eating and had prolapse of the rectum before it died totally paralysed on the nineteenth day; another developed paresis on the fifty day, which persisted until it was killed on the fourteenth day when nothing abnormal was found in the nervous system. The CSF from

these rabbits injected into other animals produced no symptoms or lesions.

3. Marinesco[68] (1919) injected CSF from two patients into six guinea pigs. Four were unaffected while two which had received 1 cc. intracerebrally had difficulty in moving about after three or four days. Spirochetes were found in tissues of these two animals, but the CSF inoculated into other guinea pigs produced no result and little could be deduced from the experiments.

4. Rothfield, Freund and Hornowski[69] (1920) injected blood and CSF from four cases of multiple sclerosis into rabbits and guinea pigs. Many died but the cause of death was diagnosed to be either coccidiosis or tuberculosis; in one animal "glial changes" were found in the central nervous system but similar foci were found in other cases of coccidiosis. In all respects histologic examinations were considered negative.

5. Teague[70] (1921) appears to have carried out extensive routine investigations but was quoted by Cornwall[71] (1936) as having stated that he considered the results inconsequential and never published the findings. Descriptions of the experiments are given at length by Cornwall: The blood and/or CSF of sixteen patients with multiple sclerosis was injected into 102 guinea pigs (i.p. and i.o.), fifty-nine rabbits (i.p. and i.o.), thirty-three rats (i.p.), nineteen mice (i.p.), three cats and one dog (i.o.) and two monkeys (i.p., i.o., and s.c.). Mixtures of blood and CSF from five patients were used in separate tests but only one or the other of these fluids from the remaining eleven. There was considerable variation in the grouping of animals and in the periods of observation, which lasted up to one year but the results were considered negative as a whole. Coccidiosis was observed in some of the rabbits; pneumonia caused death in some guinea pigs. Macroscopic examinations of the central nervous system revealed no lesions in any animal; histologic examinations of the nervous system of twenty-four guinea pigs and twenty rabbits from Teague's[70] experiments were made later by Cornwall[71] (1936) but were unproductive of any positive result.

6. Birely and Dudgeon[72] (1922): The inoculum consisted of filtered suspension of brain and cord (F, nineteen years, with duration of disease about four years, Queen Square National Hospital, London). Three rabbits were inoculated, two intracerebrally and one intraperitoneally. One was observed for nine weeks and the others for five months; no symptoms were shown and no lesions were found in the pons and mid-brain of one and in the brain and cord of others. The inoculum in a second experiment consisted of CSF and blood serum (M, duration of disease of one year). Two rabbits injected with one or both fluids (i.p. and i.c.) were observed for three to four months with no signs of paralysis and no lesions in the central nervous system. The CSF and/or blood serum from thirteen other cases was injected into rabbits along the course of the sciatic nerve (also by intrathecal, intravenous, intratesticular and intraocular routes), and the animals observed for variable periods without development of neurologic signs or lesions; at the most, some transient pareses were noted in two guinea pigs. The authors concluded that their attempts to transmit infection had been unsuccessful and that other claims were unproved; they were severely critical of the experiments and the positive results reported by Bullock[73] in 1913.

7. Claude and Alajouanine[74] (1924) used material (F, twenty-three years, duration of disease about four years) in which the diagnosis was confirmed at autopsy and full pathologic descriptions were made. Pieces of cord (said to show diffuse acute myelitis), mid-brain and bulb were mixed with sterile glycerine and injected intracerebrally into six rabbits. They showed no nervous signs within four months; two were killed, revealing no lesions in the nervous system.

8. Collins and Noguchi[20] (1923), in a meticulous investigation designed to probe the spirochetal theory, presented negative evidence. The blood and CSF from eight patients with variable duration of disease was mixed and injected by a combination of routes (i.c., i.p., i.v., intratesticular and intraocular) into rabbits and guinea pigs. The results were negative both for spirochetes and for evidence of virus transmission.

9. Hudson and Grinker[75] (1933) used nervous tissue removed at autopsy from a well documented case of multiple sclerosis (F, twenty-two years, duration of disease about six years). Portions of cortex and pons were ground separately in a sterile mortar with sterile broth; intracerebral injections were made into three monkeys, while pooled portions from both sites were injected into a fourth monkey, one rabbit and three guinea pigs (i.p. and s.c.). The

laboratory animals were alive after a month and the monkeys showed no signs after twelve months; lesions were not found in the nervous system.

10. Cestan et al.[76] (1934) injected CSF and blood as quickly as possible after the fluids were withdrawn (F, thirty-three years, duration of disease four months, with history given), and from fourteen other cases, into twenty monkeys, eighty rabbits and twenty rats by intracerebral, cisternal and intraperitoneal routes. The observations covered many months and were concluded to be negative. Rabbits showed no abnormalities; two monkeys showed transient neurologic manifestations but no distinct sclerotic plaques were found in the nervous system.

11. Cornwall[71] (1936), in one instance, injected CSF (2 cc.) from one patient into a Macacus rhesus, a rabbit and a guinea pig (i.p.) and observed them for one month with negative results. Later he injected blood from eleven patients into a total of seventy-three rabbits, and the blood of eleven normal control human beings into twenty rabbits; observation of the animals ranged from one day to four years. Ten of the seventy-three and one of the twenty showed unspecified neurologic signs; in one animal small perivascular lesions of reputed demyelination were found. He concluded, like Teague, that there was no proof that a virus was concerned in multiple sclerosis.

Positive Results

1. Bullock[73] (later Gye) (1913) published results which received much publicity; he claimed that no experimental work had been done previously. Bullock inoculated CSF (kept in an ice chamber for twenty-six hours—from F, nineteen years) into a cat (intradurally) and observed it for nine weeks without any positive sign of illness being shown. A rabbit was injected subcutaneously (2 cc.) near the sciatic nerve; on the twelfth day it was suddenly paralyzed, incontinence of feces and urine followed on the fourteenth day and it was killed on the sixteenth day. Pathologically there was stated to be fragmentation of myelin sheaths, mainly in the cervical lumbar cord, but no areas of blackened fibers in Marchi preparation! The blood from this rabbit was innocuous to another. As a result of this "success" attending the first inoculation, further experiments were performed. Three rabbits were inoculated with the same CSF (ice box fourteen days): one broke its leg on the thirteenth day and was killed, the second remained healthy for nine weeks and the third became paralyzed on the twenty-first day, but not severely so, and in seven days recovered. Three weeks later it was reinoculated with the fresh CSF from the same patient and up to five weeks there was no sign of paralysis. A fresh supply of CSF (same case) was obtained in two lots (one filtered, the other not) and injected (1.5 cc.) into two rabbits subcutaneously. On the twenty-first day the rabbit receiving filtered fluid became paralyzed, and on the twenty-second day the second animal which then recovered was slightly paralyzed on the thirty-seventh day and thereafter remained healthy. The first rabbit became progressively worse, locomotion became impossible, then it recovered in six weeks but moved with a laborious spastic gait. Histologic examination (W.-Pal and Marchi methods) revealed "great areas of degeneration" throughout the cord but the brain was practically unaffected. The blood from the same patient injected into another rabbit was inactive in an eight-week period. A repeat experiment with CSF from another female patient (twenty years—six months' duration of disease) into rabbits was negative (rabbits died in ten, fourteen, twenty-one and twenty-six days). There is a subsequent statement that paralysis of the hind limbs was produced in four rabbits by injecting CSF subcutaneously (potent after being kept at 0°c. fourteen days), and histologic examination of the spinal cord revealed a complete reproduction of lesions found in human subjects. (The illustrations purporting to show the pathologic changes are of little worth for they are crude drawings.)

The same author[77] (now Gye, 1921) returned to similar investigations. The CSF from twenty-one human cases (all Wassermann-negative) was injected into a total of 129 rabbits and 15 guinea pigs. The latter remained in good health and never showed any paralysis. Seventeen of the rabbits became ill and paralysed and 112 remained in good health; six (?) of those died from undetermined causes. The CSF from a patient (F, eighteen years) injected into four rabbits caused weakness in the forelimbs of one. This condition became rapidly worse but no histologic examination was reported. The CSF of this rabbit injected subdurally into another produced no result while tissue from the brain and cord injected into four rabbits (i.p.) pro-

duced no disease; one rabbit died from coccidiosis in five days and another died suddenly with no paralysis in nine days, but no histologic examinations were made. The brain and cord of this animal were injected into two other rabbits, one remaining healthy and the other dying (with no symptoms stated) in forty-two days. Four rabbits injected with brain emulsion from this last mentioned animal remained in good health and were killed three months later; no results of histologic examination are given. The general conclusion was that, in two sets of experiments, one of four and one of six rabbits became affected after CSF injections and that brain emulsions from the paralyzed animals produced a similar illness, and that this passage of infection was carried through four series; "consequently the simplest explanation was to assume the existence of a living virus."

2. Steiner[15] (1917) injected 1 cc. of CSF of a case[78] (Kuhn and Steiner, 1917) into an ape which remained well for eleven months, then developed transient spastic weakness of the lower limbs and was killed five months later. It was considered that the lesions were like those of multiple sclerosis but warning was given against hasty conclusions. The lesions described conform to what is now regarded as spontaneous leuco-encephalomyelosis.[27,54]

3. Adams et al.[79] (1923–24) inoculated CSF from nine human cases, and in five of sixteen rabbits produced nervous symptoms. Of the nine specimens of CSF, five were positive; three rabbits showed paralysis of the legs and two showed typical cerebellar symptoms. Citrated blood from eight human cases produced nervous symptoms in five of eleven rabbits, three of which showed permanent paralysis of the legs, one transient paralysis and one a typical cerebellar syndrome. Emulsions of CSF from the rabbits (glycerinated and kept at room temperature for forty-eight hours) produced, after injection, paralysis in one hindleg of a rabbit; in another case an emulsion in saline produced typical cerebellar symptoms. The citrated blood from one human patient (case 8) was inoculated into tubes of Noguchi's medium and the content of the whole culture (fourteen days' incubation) was injected (i.p.) into a rabbit which became paralyzed in forty-two days. It was stated that spirochetal-like structures were found. It was claimed that of the forty-two (total) rabbits, fourteen showed nervous symptoms and that the disease was capable of being passed from animal to animal and also from one animal through culture to another, (i.p. route—10/32, subdural route 0/1, subdural plus i.p. 2/6, and i.p. plus intratesticular 2/3). The period of development of nervous symptoms varied from 8 to 197 days. As some measure of evaluation of the results, it was said that spontaneous paralysis had not occurred in 200 stock rabbits for a period ranging from four months to one year (but there is no mention of the possibility of other diseases occurring). In conclusion it was stated that "the virus appeared to be present in the blood and CSF of human cases and was capable of living in the central nervous systems of rabbits; it was infective after culture, while blood and CSF from normal human beings and from patients with other diseases did not produce symptoms in rabbits." (The pathology described is not convincing; the photos of affected rabbits prove little; they might equally represent a number of different spontaneous diseases of rabbits.) The authors admit that the lesions found were not characteristic of the human disease and proceed to cite examples in comparative pathology in which the nature of the same disease process might change from species to species. (This phenomenon is well known but there are usually some points of resemblance; if this were not so then experimental work with any disease would be of little value for, if the differences in disease picture produced were so great, by what yardstick could positive success ever be measured?) Adams et al. [8] (1925) continued this investigation but the second paper was largely concerned with experiments designed to contribute toward the spirochetal theory and are of no concern here.

4. Behr[80] (1924) adopted an unusual approach. He postulated that since retrobulbar neuritis was such a frequent finding in multiple sclerosis, if this were due to an infection the pathway might be through the nasal passages and ethmoids. Washings of the latter from established cases of optic neuritis were mixed with saline and injected subdurally and intraocularly into three rabbits. A similar injection was made into one rabbit with material from a normal healthy man. In the three rabbits, after varying lengths of time, changes were observed in the papilla and there was spastic hemiplegia said to be comparable to that seen in the human disease. Little is described in the way of pathology.

5. Schükrü[81] (1935), after withdrawing CSF

from a rabbit cisternally, replaced this with CSF from a human patient (disease of three years' duration). Immediate symptoms of meningeal irritation were recorded; the animal was unable to stand and died in three days. There was no evidence of traumatic damage but lesions with myelin changes were described to occur in Ammon's horn and the pons. In a second rabbit injected with CSF from the same case, necrobiotic and hemorrhagic changes were found in the occipital lobe, the cerebellar cortex and pons. In a third rabbit injected with CSF from another human case (four years' duration) there were no marked changes. In a fourth rabbit, killed at six months, demyelinated foci with gliosis and perivascular infiltration were described. It was concluded that the experimental disease was the equivalent of multiple sclerosis.

6. Schaltenbrand[1] (1943) deserves particular attention but it is not possible to give details of his extended protocols here. Apart from experimental work, he deals with other aspects of the disease, starting with geographic distribution in Germany. (Because of the method of selection of cases the distribution in Southern Germany cannot be said to reveal any focalization of cases.)

Attempts were made to transmit multiple sclerosis from man to monkeys by using CSF and nervous tissue. After positive results were obtained, but not constantly so, the project was carried over to the transmission of the disease from monkey to man and from man to man (using cases of catatonia and schizophrenia in an asylum). It is sufficient to state that in the monkey a disease process was "produced" which Schaltenbrand admitted could not be distinguished from the spontaneous leucoencephalomyelosis of monkeys. Scherer and others criticized the work from this and other angles; other authorities suggest that Schaltenbrand may have produced iso-allergic encephalitis. His work, of course, was done before the observations of Kabat et al. (1947). Fresh and filtered CSF from documented human cases of multiple sclerosis, after cisternal injections in monkeys, caused a pleocytosis up to 300 times above normal which lasted for about six months, and returned to normal. Some animals developed signs of paresis and showed changes in the central nervous system mentioned above. Secondary anemia was sometimes present. The disease was also observed to be passaged from monkey to monkey by contact in the same room (other reasons for criticism by Scherer). In the human experiments changes were found in the CSF comparable to those seen in monkeys plus signs of fever, which were taken as an index of transference of infection. Schaltenbrand reasons that the "virus" in man must be endemic and widespread but that most human beings must be resistant or show only transient subclinical symptoms of some obscure febrile condition. He cited examples of such transference in doctors, nurses and others in contact with cases of multiple sclerosis in wards, and also records of some sibling cases.

7. It is unfortunate that the attempts by foreign workers to obtain strains of the viruses (Sv and Ef) isolated by Margulis, Soloviev and Shubladze[2] (1946) failed completely. Many questionable features regarding their claims of specificity of virus infection might then have been investigated. Nevertheless, the work described by them cannot be ignored and additional experimental work would be desirable in connection with multiple sclerosis.

Two strains of virus were isolated and identified as being different from any other known neurotropic virus of man or animals. One strain—(Sv)—was isolated from the blood and CSF after the second passage through albino mice. The donor patient (M, thirty-two) of this strain had a remittent neurologic illness, lasting from November, 1942, until June, 1945, which was diagnosed as acute disseminated encephalomyelitis. The second strain (Ef) was obtained from the nervous tissue of a patient (F, thirty-eight) with an acute, febrile and fatal neurologic illness lasting nine days; it was isolated at the first passage by intracerebral inoculation into mice. The murine encephalitis differed from herpes, showed miliary foci of necrosis and demyelination but no inclusion bodies. The viruses were transmissible to rabbits and puppies in which demyelination was more evident than in guinea pigs and in rats in which necrosis was more prominent. In mice the incubation period was about ten days when tremors were noted, then transient clonic convulsions, while in the larger animals paralysis occurred. Puppies and mice showed the greatest susceptibility. Attempts to isolate any virus from the CSF of cases of *chronic* multiple sclerosis were unsuccessful. Both strains of virus were neutralized by the sera of patients who had recovered from acute disseminated encephalitis, and a similar result was obtained in twenty-five

of fifty patients with multiple sclerosis, but in only one of twenty-seven patients suffering from other nervous disorders (this one case having been diagnosed as vestibular encephalitis). Neither strain of virus was neutralized by sera from cases of Russian spring-summer encephalitis, or *vice versa*. The authors emphasized, in any event, that there was no clinical, epidemiologic or anatomic resemblance between the acute encephalitis (described by them) and the tick-borne type in Russia. There is a lengthy discussion on the relationship between acute disseminated encephalitis and multiple sclerosis which to some extent has been dealt with above. The authors take a strong view on this but state that, although the identity of etiology would not necessarily imply transition of the acute disease into a chronic one, tick-borne encephalitis seldom develops acute progressive forms in the Far East whereas in the West it frequently takes a chronic course. We believe that these observations are provocative at least, providing pointers for further work on the same lines in other countries.

COMMENTS

None of the evidence offered for or against a viral origin of multiple sclerosis is irrefutably conclusive. That which can be brought up from the standpoint of the clinician or pathologist serves only to raise many other unanswerable questions. A consideration of the classification of the demyelination diseases reveals our inability to group them except on a most tentative nosologic basis. Indeed, as King and Meehan[38] point out, there is danger in this for it might cause a cloak of pseudo-unity to be cast over all the human maladies of this type. Experimental work dealing with the "toxic" or allergic type of demyelinating diseases offer in reality little more hope at the present, except the knowledge that the lesion itself (demyelination) can be caused by many different mechanisms; none of the pathologic conditions produced are the exact counterpart of human multiple sclerosis. Analogies taken from animal pathology portend that demyelination can be caused by viruses, which by itself is most important for it reverses a view held some years ago. Our review of the experimental attempts to transmit multiple sclerosis to laboratory animals produces no more tangible positive or negative proof, for there are too many limitations placed upon work of this kind. A number of such published studies may have been missed or were impossible to obtain but probably none of these would have changed our general conclusions.

The reported experimental studies will not be discussed separately, but rather we will discuss some of the criteria which might invalidate results in experimental work of this kind, either in a positive or negative sense.

Donor of Inoculum. When negative results are reported, one may question whether the donors actually had multiple sclerosis, and in some cases the clinical data given might be regarded as inadequate. Complete histories indicating that classical cases of multiple sclerosis were used, however, appear in the protocols of some experiments producing both positive and negative results.

Type of Inoculum Used. A virus causing a nervous disease might not be present in the blood or cerebrospinal fluid at all stages of illness; this is well demonstrated in diseases such as poliomyelitis, louping-ill of sheep and some forms of canine encephalitis. In a disease of such remitting chronicity as multiple sclerosis any causal virus might reasonably be assumed to be present in the nervous system (or blood and CSF) only during the primary attack and subsequent exacerbations. It would thus be important to have records which would indicate *when* in the course of the disease blood, CSF or nervous tissue was taken. In the case of nervous tissue (after autopsy) it would also be advantageous to know how it was treated prior to inoculation and by which routes it was inoculated. These considerations alone might raise some doubts as to the validity of many reported negative results. On the other hand, positive results might sometimes have appeared, not as a result of a transmissible agent, but because transient neuroparalysis, or fatal encephalitis, developed as an allergic response to inoculated nervous tissue. These pitfalls might conceivably be avoided by careful pathologic examination of the nervous system of all experimental animals.

Experimental Animals. The negative experiments have never been extensive in the sense of the numbers or species of animals used. The species used have been limited to rabbits, guinea pigs, monkeys, a few dogs and cats and, occasionally, rats and mice. Teague's[70] study was about the only one in which a large variety of test animals were used. The only conclusion which might be drawn from the earlier ex-

periments would be that with the restricted types of inoculum, with the small number and limited species of animals used, passage of a virus was not proved.

If multiple sclerosis were caused by a virus, it might be highly host-specific. For viruses to be identified as transmissible agents they must overcome species resistance, structural blockades, antisera, inhibitors, interference phenomena and so on, and they must find a susceptible cell in a susceptible host. In the case of multiple sclerosis the crux of the matter might be the latter, just as in distemper no advance was possible until the susceptibility of the ferret family was discovered.

Improvements in laboratory technics plus the chance (or ingenious) selection of animal species for transmission experiments have made it possible for workers to identify "new" viruses, while the wide use of the chick-embryo technic has altered views on the problems of adaptation. Dalldorf[82] (1950) mentions how better technics for transference of viruses to species other than the natural hosts might yield surprising results. He cites how rinderpest (host-specific for ruminants) and hog cholera (host-specific for swine) have been adapted to rabbits by alternate passage in resistant and susceptible animals. He also indicates how age of the animal used might make the utmost difference because barriers to the spread of certain viruses develop with increasing maturity, (c.f., the work done in recent years on the Coxsackie group). Another consideration is the possibility that dual infections may play some part in pathogenesis (as, for example, tick-borne fever preceding louping-ill virus encephalitis in sheep, or the swine influenza virus and its association with the lung worm as well as Haemophilus influenza suis (Shope,[83] 1950).

Evaluation of Results on Symptoms and Pathology. The possibility of spontaneous infections being responsible for coincidental nervous symptoms and disease in the "positive reports" should be considered. The use of the word "paralysis" in protocols is insufficient to convince the reader that an animal was suffering from a true neuroparalysis, least of all like that in multiple sclerosis. There are many conditions of laboratory and domestic animals (in which neurologic examination is difficult enough) in which simple bodily weakness would prohibit locomotion and ostensibly paralyze the animal. (A notorious one in rabbits is enteric coccidiosis.) In the monkey the occurrence of the spontaneous leuco-encephalomyelosis, with the pathologic features similar to experimental simian allergic encephalitis, must be remembered. In the dog the widespread enzootic occurrence of varieties of demyelinating encephalitis, one at least caused by a virus, would render experimental investigations on multiple sclerosis of doubtful value unless the animals were rigorously controlled. Evaluation of results by symptoms would thus be risky and pathologic examinations of all experimental animals highly necessary even perhaps in cases in which no nervous signs had appeared.

Work done on allergic encephalitis in guinea pigs[12,84,85] showed that animals might survive for long periods before the onset of disease; and although neurologic signs might be transient in character, or absent, pathologic lesions were found in the nervous system. In some sheep experiments by Innes[13] (1951) a very lengthy latent period (over 100 days) elapsed before the onset of nervous signs. In some sheep there was evidence of remission of symptoms. All these features would indicate that the period of observation in experimental work on multiple sclerosis might have to be lengthy. The need for careful pathologic examination of animals is obvious.

It would appear that further investigations are required to study more thoroughly the question of a possible viral origin for multiple sclerosis. This is supported somewhat by the work of Schaltenbrand[1] (1943) and Margulis, Soloviev and Schubladze[2] (1946), even though both of these contributions have been severely criticized by some authorities. Our opinions might further be weighed in the balance with those of eminent neurologists who have reviewed all aspects of multiple sclerosis, notably Guillain[86] (1924), Russell Brain[23] (1930), Kinnier Wilson[24] (1940) and McAlpine[4] (1946). The views of the last three are in harmony. Kinnier Wilson stated "that the disease may be caused by a filterable virus is at present little else than conjecture, but since no visible organism has been discovered, and for reasons outlined a toxic or toxi-infective agent seems plausible . . . the view is not to be lightly dismissed . . . pathological and other evidence is in favour of a neurotrope. . . . Though it is true that negative results [which the present authors think have a limited significance] tend effectively to outweigh positive results, positive trans-

mission cannot be overlooked, but in no case so far has the reproduced disease borne the characteristics of polysclerosis clinically, nor have the lesions been identical."

It is not the concern of this paper to outline the type of experiment required, but many points in this direction have been mentioned.

CONCLUSIONS

1. The etiology of multiple sclerosis remains as vague today as it was in Charcot's era.

2. From clinical evidence alone it is impossible to produce tangible proof either for or against the theory that multiple sclerosis may be caused by viral infection.

3. Pathologic studies have too many limitations to permit valid argument that the disease is or is not due to a virus. The history of the demyelinating diseases in man and animals indicates some dangers in postulating a specific cause (infective or other) from the nature of the essential pathologic process, that is, demyelination.

4. The demyelinating encephalitides produced in varied species by disparate types of "poisons" (or by injections of brain emulsions) are not strictly comparable to multiple sclerosis. It is thus difficult to see how such induced processes will assist in elucidating the cause of the human disease, unless it was, as E. Müller[87] (1904) originally considered, idiopathic. This type of experimental work might help in clarification of the mechanism of myelin destruction but this need not necessarily be the same in a spontaneous disease such as multiple sclerosis of man.

5. With few exceptions, all experiments designed to answer the question of infectivity in multiple sclerosis have a restricted value. No specific virus has been unequivocally demonstrated and confirmed. Many of the investigations indicating absence of infectivity are so limited as regards source of material, laboratory animal species, and technics used, that conclusions from the data presented are not wholely admissible. If multiple sclerosis were due to a virus, it might be strongly host-specific. There are many instances in the general field of virus diseases which call attention to the difficulties attached to the transmission and adaptation of a virus to *unnatural hosts*.

6. The virus hypothesis is still neither proved nor disproved, and reinvestigation seems justified. In the event such studies are made, valuable lessons may be learned from existing knowledge of the spontaneous diseases of man and domesticated animals, of experimental encephalitis in laboratory animals and of the natural history of established virus diseases. Attention might then be drawn to: (1) the need to include work on acute disseminated encephalitis, on neuropticomyelitis (Devic) and diffuse sclerosis (Schilder's); (2) utilization of animals outside the range of the common laboratory species, suckling and older animals, and perhaps domesticated animals such as lambs and dogs; (3) the advantages of working with pure strains of animals bred from disease-free stock; (4) the dangers of intercurrent nervous diseases in experimental animals which may invalidate results; (5) the need for pathologic examinations of the nervous system of all experimental animals which show signs of nervous disease and (6) constant consideration of the possibility that, in view of biologic differences between man and lower animals, even if a virus were found, it might not evoke in animals a disease exactly like multiple sclerosis.

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Personality Structure and Psychotherapy in Multiple Sclerosis*

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THERE are undoubtedly differences of opinion concerning the value of psychotherapy in the treatment of multiple sclerosis. We support the importance of psychotherapy for three reasons. The first can be stated briefly. Psychotherapy, either intensive or supportive in nature, constitutes the only possible general treatment for this disease, for which no specific remedy is yet known. The second argument is a more positive one. Psychotherapy can aid a patient to deal more realistically with any severe physical handicap. All men struggle throughout life toward a greater emotional maturity which will help them meet the vicissitudes of life with some equanimity. The most stimulating manner of considering chronic disease is to think of it as a challenge to greater emotional growth on the part of the patient. It can be postulated that the disability accompanying the disease is less, the greater the degree of emotional maturity. There is evidence that emotional growth occurs not in the pleasant periods of life but when stimulated by difficult and distressing situations. Anxiety is the stimulus that pushes men to grow and to overcome life handicaps. The psychotherapist can guide a patient toward emotional growth.

The final reason to advocate psychotherapy has to do with its usefulness in obtaining more information about the disease itself. Psychotherapy offers an opportunity to learn a great deal about patients as persons. Do certain persons have problems in interpersonal relationships bearing on the onset of the disease? Is there an emotional causative factor in the onset of the organic symptoms of multiple sclerosis? Do the handicaps of the organic disease change the personality in any profound way and is this change somewhat similar in a group of multiple sclerosis patients? Do periods of emotional stress precede exacerbations of the disease? Finally, it is important to learn whether psychotherapy can have any value in relieving the exacerbations of the disease. The importance of any treatment of the organic symptoms is extremely difficult to evaluate. However, the psychotherapeutic approach opens a whole new field of investigation which has been given relatively little attention. It would appear to merit a great deal of study and consideration.

The subject of psychotherapy in multiple sclerosis may be introduced by a case report. This report is oriented to show the attitudes which this patient uses in relating herself to other people. It also indicates possible emotional factors related directly to the onset and exacerbation of organic symptoms. Finally, it presents the factor of psychotherapy in relation to an acute exacerbation of the disease. Although this patient has developed organic symptoms at least three times in the last seven years, she has been practically free from any organic handicap during most of this time. She was also well when she left the hospital recently. These mild and early cases of multiple sclerosis with clear-cut remissions and exacerbations seem especially favorable for a study of related emotional factors. They do bring up a problem of differential diagnosis between conversion hysteria and multiple sclerosis.

CASE REPORT

The patient (Mrs. B.) was a forty-seven year old housewise. She was an illegitimate child, adopted during the first year of her life. Her foster mother was a domineering woman and the foster father a more passive individual whom she considered warm and understanding. She believes she would not have survived her childhood without his support. The patient's childhood was characterized by frequent arguments and fights with the mother who often slapped her in the face. "If she disciplined me, dad would disagree and then mother would jump on him

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just as she did on me. Sometimes she wouldn't talk to either of us for as long as ten days." The mother would tell her what a bad girl she was when the patient would stand up to her and say, "I hate you." In telling about the parents' relationships she said, "I'm sure a great deal of the difficulty that mother and dad had was over me. Mother thought sex was sinful and I was never told a thing." Early in her life she developed severe symptoms of asthma and hayfever. These difficulties served to keep her isolated from play with children of her own age.

The patient finished college and married at the age of twenty-two. At the request of her parents her husband told her about sex after they were engaged. Mrs. B. said she had thought that the marriage was for companionship and she had not thought of sex. She described the marriage as wonderful. There were three children. Recently she was disturbed when she learned that her older son's fiancee was pregnant. This stirred up her feelings about her own illegitimacy. "I was pretty disappointed in him. I felt that he had let me down." Her daughter of fifteen has a rebellious attitude toward her. "She picks and picks at me. Nothing I do is right. I know I could never criticize my mother like she criticizes me."

Her first symptoms of multiple sclerosis developed in 1943 when her husband went overseas. She tells the story in the following way: "I felt my life was over. I couldn't see how we would be a whole family again. I never told him how I felt as I didn't want to bother him. I cried all one Sunday. At the time he left I had the "flu" and I was in bed for three weeks. I felt light-headed as if I were blacking out for a minute. I had hot flushes and I was very tense. My left arm became weak and my left leg began to drag. It took several months for this to clear up." She was first studied in the hospital in 1948 when she developed a facial paralysis on the left and complained of weakness of the left arm and leg. There appears to have been mild loss of function of all the muscles innervated by the left facial nerve. The left hand grip was weak. The deep reflexes were more active on the left and there was an equivocal left Babinski reflex. The abdominal reflexes were less active on the left. Spinal fluid examination revealed no abnormalities but a colloidal gold test was not done. The diagnosis of multiple sclerosis was made at that time. After two weeks in the hospital she was discharged in good health. When questioned recently she was able to give a story of emotional crisis preceding this illness in 1948. "My husband was very tense and not himself at all after he had had a physical examination. He would evade any question I might ask." She called up a doctor friend who told her that his electrocardiogram was abnormal and that he might have heart disease. Shortly afterward her husband went to the hospital for a hernia operation. "He wouldn't tell me when it was going to be because he didn't want to worry me. One day I felt something was wrong and I called up the hospital. They said that he had just been operated." When her husband came home to convalesce from the operation, she was caught in great responsibility. Her tension increased and she had a severe attack of asthma. She felt fatigued, dizzy, nauseated and could hardly keep her balance; she then developed the left-sided weakness.

The data concerning her recent illness in 1951 are more detailed since the emotional factors were studied at the time. Many disturbing events occurred together. In February, 1951, her foster father became ill and died in March. She did not go to see him when he was ill, "because I knew he would not want me to see him that way." In April she attended her son's wedding. This marriage was hastened because the bride was pregnant. Mrs. B. then went through a period of great tension with her mother when she tried to close her mother's home and dispose of her possessions. "I didn't know how to handle mother. One time we had a knock-down-drag-out fight. When you have to talk cruel to your mother, that shouldn't be. I felt guilty then and I still do. I had headaches and I was just frantic; I was nauseated." About the first of June the mother came to live with the patient and relationships became even more strained. "She started to do the dominating and bossing and would sulk when the children were there. She insisted that we take our furniture out and put hers in. She got my daughter in tears because she said that I had no taste and our house was a hut and a shack. I heard her tell my husband that I was always bad and that there was no good in me. I felt something was going to break. I could not stand the pressure in my head much longer. I had to have some relief from the headaches and tension." At times she would get her husband to talk with the mother in an effort to improve the situation but she had difficulty in telling her husband her real feelings.

The patient's tension increased until she entered the hospital in August. She had increasing irritability toward her husband and daughter. She felt guilty about this and felt that she was harming them. She became less interested in sexual relations and indicated to her husband that she did not want to have intercourse. He was indifferent to her after that and this disturbed her more than anything, as she was so dependent upon him. A few days before coming to the hospital she awakened with a feeling of nausea and dizziness. A few hours later she began to see double and developed a feeling of heaviness in her left arm and leg.

On examination the patient gave evidence of a great desire to please. She showed a marked degree of asthenia and lay quietly in bed. She said she was so tired she could scarcely move. She seemed emotionally disturbed and cried easily. At first she did not appear concerned about the condition of her eyes. The principal findings had to do with the eyes inasmuch as she could not move either eye beyond the main axis toward the midline. The findings suggested bilateral paralysis of both internal rectus muscles. All other movements of the eyes were normal except for some slight nystagmus in looking to either side. Other neurologic findings were minimal. The deep reflexes seemed more active on the left and there was a questionable left Babinski reflex. Spinal fluid showed a total protein of 44 mg. per cent and a first zone colloidal gold test.

Although Mrs. B. talked very freely and with emotion about the difficult family situation, it was believed that a more active psychotherapeutic approach would be of greater benefit and a pentothal interview was planned. When Mrs. B. was told of this, she showed much anxiety about losing control of her feelings and indicated that she might say or do something she did not mean. She called her husband and insisted that he be present and became quite disturbed when he was asked to leave the room during the pentothal interview. Mrs. B. then talked with a flood of emotion concerning her extreme dependence upon her husband and said that there would be nothing to live for if she would lose him. She said that she felt guilty, feeling herself a severe burden to him because of her disposition. She explained that she was like her mother, irritable and demanding, and believed that this was injuring her husband. She expressed an attitude that her mother was good and it was only because of her own badness that her mother was irritable. The main feelings brought out in the interview were the patient's guilt and identification with the mother.

When Mrs. B. was seen two days later she was more relaxed and said that she had noticed an improvement in her eyes. During the remainder of her stay in the hospital she maintained that her mother was a "dear person." Within a few days the eye movements became normal. Strength returned rapidly and the patient felt well when she left the hospital.

Comments. This patient was related comfortably to persons close to her only as a dependent individual. A good relationship was evident with her foster father and with her husband. With other people such as her foster mother and daughter she appears to have been aggressively hostile and to have been beaten down by them in return. Before coming to the hospital for her last visit she showed some passive aggression toward her husband in refusing to have sex relations. Her husband's withdrawal of his protective role toward her may well have been a large factor in precipitating the last illness. Symptoms of asthma are frequently observed in patients who feel the need of a highly dependent relationship to the mother and it is quite probable that Mrs. B. needed this relationship which was denied. Her continued illnesses in childhood served to maintain some thread of a dependent relationship with the mother. The pentothal interview brought out clearly the patient's guilt and the feeling that she was injuring her husband and children by her attitudes. She had an awareness that her own irritability and demanding nature were similar to her mother's. With the doctors she assumed the dependent, eager-to-please attitude of a child. Obviously she showed great emotional immaturity.

In reviewing this story it must be remembered that the emotional factors in the illness were considered only at the time of the patient's last visit to the hospital. The story of the onset of the illness and the circumstances leading to the first admission to the hospital were obtained only in retrospect. These two periods of illness appeared to have occurred at times when she lost her dependent relationship to her husband. The first time he went away and the second time she felt that he might be incapacitated or taken away by illness. During the first of these periods we know that she made some effort to control him and to keep him from leaving. Thus she

tells us that she cried one whole day and she was sick in bed when he left. We have our best picture of the turmoil preceding the last bout of illness inasmuch as information was obtained at the time. All her relationships with people close to her deteriorated simultaneously. She lost her father on whom she could depend. Her son disappointed her by making his fiancee pregnant and reminding her that she was illegitimate. Her daughter had been rebelling against her. The mother moved into the home and was in a dominating position from which the patient could not escape. She tried to retaliate against her husband whom she thought did not help her enough and seemed to lose his support. In the pentothal interview she brought out her certainty that she was destroying her husband, the very person she was so greatly dependent upon, by her behavior which she likened to her mother's. In this setting her tension mounted and the symptoms appeared.

It should be mentioned that she had influenza when the illness first began in 1943 and a severe attack of asthma before she entered the hospital for the first time (1948). During this first hospital period she was investigated from the standpoint of allergy. There are suggestions that allergic reactions may be a factor in the onset of multiple sclerosis.

Any evaluation of treatment in multiple sclerosis is difficult because the early signs and symptoms tend to disappear spontaneously independent of any efforts in therapy. In the case which has been described the pentothal interview released a flood of emotional material. Within a day or two thereafter the eye movements improved. Very little stress can be placed on the relationships of these phenomena. It is clear that the emotional catharsis relieved much of the patient's tension. Thereafter she tended to view the home situation with some equanimity. Perhaps one of the main factors in her improvement could be attributed to her husband taking a strong supportive role following her admission to the hospital. He made immediate arrangements for her mother to be placed in a nursing home.

It would be difficult in this case to support with complete assurance the diagnosis of multiple sclerosis rather than conversion hysteria. The diagnosis of multiple sclerosis had been made on a previous admission and we saw no special reason to disagree. Each time the patient became ill she complained of weakness of the extremities on the left and there were slight objective findings each time of loss of corticospinal control, manifested as increased deep reflexes on the left, diminished abdominal reflexes on the left and a suggestive left Babinski reflex. The colloidal gold test on the spinal fluid was positive at the time of the last admission. On the other hand, we find it hard to explain on an anatomic basis the inability to turn either eye inward past the midline. A midline lesion in the mid-brain might produce such a finding but certainly this particular difficulty is rare. The eye signs are suggestive of conversion hysteria. In favor of an organic lesion (1) the pupils became smaller when the patient was asked to converge even though the eyes did not turn in and (2) strong suggestion during the pentothal interview did not improve the eye movements. The relation of multiple sclerosis and conversion hysteria will be discussed later in this paper.

PERSONALITY STRUCTURE IN PATIENTS WITH MULTIPLE SCLEROSIS

A discussion of personality trends in patients with multiple sclerosis must be approached with reservation. Obviously a psychiatrist can become intimately acquainted with only a small group of individuals so that it is difficult to collect a series of observations which is statistically significant. Moreover, the psychiatrist is likely to develop an individual bias toward the problem.

Psychologic testing offers a method of gathering statistical data concerning a large group of patients with multiple sclerosis. This method has been used by Harrower and her associates. Harrower and Kraus have now tested 140 subjects with multiple sclerosis. Control groups included patients handicapped physically with tabes, poliomyelitis, Parkinsonism, persons with neurotic difficulties and persons free from symptoms at the time of testing and designated as normal. The incidence of certain traits was significantly higher in those with multiple sclerosis than the normal control groups although individual patients with multiple sclerosis, of course, deviated widely from this pattern. Harrower found that patients with multiple sclerosis showed an overemphasis of dependency needs, a virtually complete absence of body-centered anxiety, a minimum of inner conflict or attitude of resignation, and an unrealistic tendency to see the world through rose colored glasses.

To determine whether persons possessing these traits are more likely to develop multiple sclerosis or if the actual conditions of the disease provoke these traits, these authors have studied patients demonstrating a remission of symptoms, patients with mild disease, severely ill patients living in their own homes, severely ill and hospitalized patients and a group of patients in an environment aimed at fostering independence. Characteristic of patients in remission has been a higher percentage with superior intelligence and a low percentage with erratic performance on the intelligence test. On the Rorschach test the patients in remission showed the greatest capacity for richer psychologic experience and the highest percentage of expanded personality types. The remission group also exhibited a more realistic willingness to allow the anxiety associated with physical symptoms to become conscious. Among the patients with mild, early disease a moderate percentage manifested extreme scatter on the intelligence test. The patients in whom independence was encouraged showed the lowest dependency scores and the greatest degree of extroversion. Patients with advanced disease revealed the lowest number of patients with superior intelligence, the highest scatter rate, the highest number of extreme personality constriction, the highest dependency score and a disregard of bodily symptoms. The authors consider that the changes within the group as the disease progresses make it seem unlikely that the psychologic characteristics could be considered as predisposing the person to the disease. It would seem rather that multiple sclerosis leaves its mark to a greater or lesser degree, depending upon the patient's premorbid personality.

Canter used the Minnesota multiphasic personality inventory to study thirty-three veterans with multiple sclerosis. The mean age of the group was thirty-two and the duration of the symptoms of multiple sclerosis ranged from one to eight years with an average of four years. Approximately 65 per cent had received a diagnosis of hysteria prior to the development of neurologic symptoms. Canter found that the tests revealed a reaction of depression, preoccupation and concern about bodily functions, feelings of hopelessness and insecurity as well as tendencies toward indecisiveness, narrowness of interests and introversion. Difficulty in accepting the disease and its progressive limitations as well as ambivalence and insecurity concerning the future are often reflected in relatively poor emotional control and social adjustment.

The psychiatrist has the opportunity to gather data concerning the methods which the patient uses to carry out interpersonal relationships through youth and adult years and to learn the complications of disturbed relationships. Grinker and his associates studied twenty-six cases of multiple sclerosis by the interview method. They concluded that these patients seem to have an excessive need for love and affection which is not gratified in childhood. These frustrations evoke anger which must be repressed in order to preserve whatever gratifications are available. As a result the external personality is a happy-go-lucky person with a paramount desire to please and to be approved. There seems to be outward calm and an inner tension. Relationships with other people are never close and never expressed with any degree of emotional warmth. They want to be liked by everyone without making close emotional attachments. Marriage develops no close libidinal relationships and there is no feeling of being in love with the partner. The precipitating factors for the development of overt neurologic symptoms are usually major changes in the life situation which stimulate intense resentment or anger or which demand an excessive amount of mental or physical strain. Remissions frequently occur when the patient is permitted to relax, to go to bed for a rest, or is permitted to give up some load of responsibility. After illness develops the increased dependent needs and the inevitable frustrations increase the inner hostility which brings on further defenses to increasing dependency.

Personal experiences of one of the authors (Langworthy, 1948 and 1950) have also led us to conclude that there is a special group of patients with multiple sclerosis in whom poor emotional adjustment is a problem even before the symptoms of organic disease develop. These patients are emotionally immature and show this immaturity in all their interpersonal relationships. It is often evident in their sexual adjustment, which can be evaluated at a preadolescent level of emotional growth. The diagnosis of conversion hysteria is frequently made at the onset of the symptom, not alone because of the bizarre nature of the complaints but especially because of a personality structure consistent with this diagnosis. Later, when

objective signs of organic cerebral damage appear, the diagnosis is abruptly changed to multiple sclerosis. It is probable that these patients have a tendency to conversion symptoms as well as showing the changes typical of multiple sclerosis. Conversion symptoms have been observed developing long after the organic signs of multiple sclerosis are apparent. Many patients are also aware themselves that periods of emotional turmoil tend to bring on new disabilities characteristic of the disease.

Four women with multiple sclerosis were studied carefully in a psychiatric hospital setting (Langworthy, 1948). A brief abstract of their cases was published. All of these women were caught in an entangling neurotic relationship with one of the parents. There was some evidence in each case that it was the mother. Emotional immaturity made sexual relationships unsatisfactory. All four happened to marry, in defiance of their parents, men whom they considered intellectually and socially inferior to themselves. The patients became ill when their husbands gained more self assurance and began to assume a more dominant role. Emotional problems associated with pregnancy tended to cause an exacerbation of the symptoms. While this summary statement obviously would not apply in its entirety to a larger group of individuals, it does suggest that these patients were uncomfortable when controlled and dominated by other people and symptoms were likely to occur when they were hopelessly caught in this type of situation. These four women also illustrate the fact that multiple sclerotic subjects may take refuge in a severe psychiatric reaction when the anxiety of the life situation becomes too great. One of the four women showed paranoid trends and two complained of depressive symptoms.

A later paper (Langworthy, 1950) discussed the life problems of a young physician who had probable multiple sclerosis although there was a possibility that all of the symptoms were functional. Later, after this report was published, he lapsed in treatment and moved to another city where he developed clear-cut symptoms of multiple sclerosis in an exacerbation of the disease. This man had been smothered with an overwhelming affection by his mother to satisfy her own needs which kept him from obtaining even the adolescent level of emotional adjustment. He showed a tendency to develop conversion symptoms in dealing with sexual problems. Of greater significance was the fact that he was a passive individual who felt increasing domination by aggressive persons. He was acutely uncomfortable in a highly competitive work situation. It was in relation to the problem of aggression that he seemed to develop symptoms suggestive of multiple sclerosis.

There is a tendency at present to think of multiple sclerosis as a syndrome probably induced by several factors in the life situation. There are two significant trends in current studies of the etiology of the disease. One of these lies in the field of allergy since animals may be sensitized to brain tissue, causing a breakdown of myelin in the nervous system. The other suggests a disturbance of circulation involving small vessels in the nervous system. If emotional factors influence the onset of symptoms, their effect might be exerted through changes in the circulation. At a time when new symptoms appear, patients often show signs of vasomotor instability in the extremities.

PSYCHOTHERAPY IN MULTIPLE SCLEROSIS

Physicians will be more comfortable in considering the use of psychotherapy in multiple sclerosis if they have only the limited objective of helping the patient to live more comfortably with physical handicaps. As for the possible value of psychotherapy in controlling the physical symptoms this must be considered as a matter for long-term investigative studies. For this investigative work patients in the early stages of the disease with periods of almost complete remission would seem most favorable.

In starting to treat multiple sclerosis it is useful to think that the outcome is often fairly favorable. Some individuals show periods of remission for many years after the illness begins and during their remissions they may be handicapped little if at all. A few individuals show remissions which last for so many years that to all intents and purposes they appear cured. Even when the handicap has become quite severe, the disease may become stationary. An optimistic point of view is somewhat realistic and useful to both the patient and the physician.

Although such a plan is seldom possible, probably the best setting for psychotherapy in multiple sclerosis is a clinic which specializes in physical therapy and physical rehabilitation. The patient believes that this is a sensible and realistic approach to the physical disability. Some interest in the patient's difficulties in

adjustment in interpersonal relations and consideration of his fears and anxieties fit rather naturally into this setting. It is indeed unfortunate that this type of clinic is not available to many patients with multiple sclerosis.

Probably the best psychotherapy is nondirective. It does not offer any particular reassurance nor does it give advice concerning hobbies or other activities. It allows the patient adequate time to express his feelings about the illness. The patient is grateful and appreciative of the interest and understanding on the part of the physician. This permits the patient to be more self-revealing and give some expression of his fears and anxieties related to the illness and the handicaps that arise from physical disability. This anxiety can be directed toward personal reorientation toward the situation. The patient who was considered in this report was able in the hospital setting to discuss her anxieties concerning interpersonal relationships rather freely and seemed to show a marked decrease in tension. It has been suggested that most patients with multiple sclerosis keep their anxiety well hidden behind an unrealistic tendency to see the world through rose colored glasses. At times the anxiety does break through and the setting of sympathetic interest on the part of the doctor allows them to express their true feelings. It is probably in these periods when anxiety comes to the surface that psychotherapy can be particularly helpful. Many of these patients seem to be unusually dependent persons. They have an opportunity to use a physician as a strong figure on whom they can lean in a dependent way. Symptoms appear when they feel a domination of other persons from which they cannot escape. The discussions of their discomfort in the face of aggression and domination may help them to work out a method of dealing more adequately with this problem.

During treatment it is important to keep anxiety somewhat within bounds. A gradual release of anxiety may be used therapeutically, but uncontrolled anxiety may lead to disastrous results. Before discussing different aspects of the disease with the patient it is helpful to get some idea of their capacity to deal with anxiety. Ill advised suggestions may do great harm. The following example may be given: Sometimes patients are advised to move at once to a warm, dry climate. This may necessitate giving up the security of a job and leaving relatives and friends. Such advice may lead to depressive symptoms which are more devastating than the multiple sclerosis. Similarly, a patient cannot be given positive advice to avoid pregnancy even though new symptoms often appear in women during or after pregnancy. They can be advised of the possible consequences and allowed to make their own decisions. Probably if the patient asks concerning the nature of his trouble, he should be told quite frankly that he has multiple sclerosis. Reality may be injected into the situation as the patient is able to accept it without undue anxiety.

Finally, psychotherapy offers the broadest perspective on treatment since it primarily considers the patient as a person. Within this broad plan of therapy all other possible medical or physical methods of rehabilitation can be considered and used in their proper context. The physician can feel comfortable that he is doing his best with a difficult situation.

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Problems in Evaluating Treatment in Multiple Sclerosis*

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THE purpose of this paper is to discuss several of the basic problems and common pitfalls encountered in evaluating therapy in multiple sclerosis in the light of observations made on 250 patients referred to the New York University-Bellevue Multiple Sclerosis Research Project. It is not the aim of the author to review the types of treatment in this disorder or to discuss the problem of statistical significance.

A recent treatise on the subject has described the numerous modes of treatment for multiple sclerosis.[1] Some were directed at combating a theoretic etiologic agent, some at correcting supposed vital chemical or physiologic dysfunctions, others at activating remaining normal tissue to take over function of the damaged tissue, and still others at re-educating involved parts to improve function. All have failed in terms of "cure." Many have been alleged to be "helpful" or "promising" based on "definite improvement."

Now and then claims of "miraculous improvement" implying cure have appeared in the lay press. Too often the physician responsible for these publications is "misquoted." Sometimes it seems that the decision to release the information far outweighs the probability of being misquoted.

Other "cures" are circulated verbally by patients or by relatives of patients with multiple sclerosis based on a "new type" of treatment. From experience with several hundred patients interviewed at this research clinic, it is estimated that roughly 90 per cent of the money spent for treatment goes to these so-called "cure" sources.

Reports on the therapy of multiple sclerosis that have appeared in recognized medical journals do not claim to cure this illness. As a rule, the investigators are cautious in their reports and specifically emphasize that their observations should not be taken as conclusive. They fully recognize the flaws in accurately evaluating treatment in such a complex and unpredictable disorder. Despite this, misinterpretations are common. Some physicians investigating the various modes of therapy are in clinical fields other than neurology and depend largely on subjective findings or specialized observations. Although these observations are important, the physician should not attach undue significance to statements of "marked improvement" unless other correlated objective data confirm such improvement.

PROBLEM OF EXACERBATIONS AND REMISSIONS

There are two favorite methods of "control" in the evaluation of therapy in multiple sclerosis. They are: (1) counting the number and frequency of remissions and exacerbations in a group of patients during and after termination of therapy and comparing these figures with a group of patients not under treatment; (2) using the patient's past performance as a control for the effects under treatment in the same group. The number and frequency of attacks and remissions are estimated from the patient's history, including records from physicians and previous hospitalizations.

There are several discrepancies in the utilization of these methods. In our experience it is often difficult to be definite about the occurrence of a remission or an exacerbation unless there are striking objective changes. Improved visual acuity with disappearance of the preexisting central scotoma, return of muscle strength with concomitant disappearance of pathologic reflexes, return to normal gait from one that was markedly unsteady are several examples of acceptable objective changes. Similar objective changes, in reverse, constitute acceptable evidence for exacerbations. Other

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changes, such as the disappearance or reappearance of an abdominal reflex or Babinski reflex, the improvement in performance ability of one or two motor acts, or the examiner's subjective impression that the tremor is less marked than previously are too indefinite to accept as evidence for a remission or exacerbation. We prefer to consider them as fluctuations. Fluctuations are common in all disease processes. Too often these fluctuations are considered and believed to be remissions or exacerqations. For purposes of analysis of the results of any treatment only the strictest criteria should be used.

Of the 212 patients under our observation at the New York University-Bellevue Multiple Sclerosis Research Project, in only twelve were we certain that a spontaneous exacerbation took place and in only twenty that a spontaneous remission occurred. The remarks of the other patients in this series inferring subjective improvement or recession could not be confirmed after careful neurologic examinations.

Comparison of the number of remissions and exacerbations based on the patient's history (including reports from other physicians and previous hospitalizations) with the number of remissions and exacerbations during and following termination of treatment also leads to erroneous conclusions. The range in the number of attacks and remissions in two groups of fifty patients without treatment, using these criteria, showed such great differences that it is evident that the patient's past performance cannot be used as a guide to improvement following therapy.

	Remissions	Exacerbations
Group I—50 patients (without treatment)	72	158
Group II—50 patients (without treatment)	114	290

Also, our experience in regard to frequency of attacks (according to history) showed that the majority of patients in our series had their greatest number in the first three years (69 per cent). Thereafter, their condition remained stationary, with or without fluctuations, and with only an occasional severe exacerbation. The remainder of the patients had attacks with long periods of remission, lasting from three to fifteen years (16 per cent) or had a slowly progressive course with no evidence by history of ever having had a remission (15 per cent). Therefore, to say that a group under treatment is having less frequent attacks also is not significant. Too often, daily or weekly fluctuations in the patient's condition are accepted as frequent remissions and exacerbations.

PROBLEM OF THE PSYCHOLOGIC EFFECTS OF THERAPY

The majority of patients with multiple sclerosis studied in this series were extremely anxious about treatment, any form of treatment, and despite repeated disappointments met each new prospect with fresh hope and overwhelming enthusiasm. It is upon this fact that some forms of therapy flourish long after they have been proved to be ineffective by the medical profession. The temporary subjective improvement and accompanying improvement in performance ability can be great in the early part of therapy. However, this wanes rapidly. "Improvement" may take place prior to the onset of therapy, depending on the confidence and dogmatic statements made by the person who is to administer it.

A small group of patients showed a reactive depression to their illness and the mere initiation of therapy produced a temporary lifting of this depression with concomitant improvement in performance. This usually is followed by a prompt return to their previous mental and physical states. At times the depression becomes more severe.

Others have a strong tendency to deny illness. This may be part of the picture of euphoria. They continually maintain that they are in good health except "for a little tremor," etc., and that "just a little treatment" is all that is needed to set them "perfect" again.

Too often these psychologic factors are not taken into consideration or not enough significance is attached to them when evaluating patients under treatment. This, together with the unpredictable spontaneity of the disease, either in the form of a remission or exacerbation, beclouds the entire issue of evaluation.

PROBLEM OF DIAGNOSIS

Frequently a reliable history alone, especially one including an attack of "blindness" in one eye, makes the diagnosis of multiple sclerosis probable. Evidence by neurologic examination

of the existence of more than one lesion plus the laboratory evidence (cerebrospinal fluid, myelogram, pneumoencephalogram, etc.) that no other condition is present clinically confirms the diagnosis. As has been stated previously, a history of remissions and exacerbations is not always obtained and when it is may be exceedingly difficult to interpret. It should be pointed out that the history of persons with neoplasm of the central nervous system often includes attacks and remissions, for example, transient paresis, sensory disturbance, etc. Therefore, unless the history plus the examination give indication of more than one lesion, the diagnosis of multiple sclerosis should be only suspected. These patients are not good candidates for research in therapy.

It behooves investigators, especially those in fields other than neurology, to be exceptionally discriminating in the choice of multiple sclerosis patients for therapy. Fifteen per cent of the 250 patients referred to this research clinic with the diagnosis of multiple sclerosis proved not to have the disorder. Among the other conditions encountered were spinal cord neoplasms, amyotrophic lateral sclerosis, posterolateral sclerosis, herniated cervical disc, Parkinsonism, cerebrovascular disorders and psychoneurosis.

COMMENT AND CONCLUSION

These are but a few of the pitfalls in evaluation of therapy in multiple sclerosis but they demonstrate the futility of accurate judgment of the effects of therapy from the clinical standpoint. Attention has been focused on these problems by others[2,3] but, in view of the continued misinterpretations and "false hopes" derived from reports on therapy, re-emphasis is in order. The inevitable question that arises is "How do we know that changes were due to the treatment under investigation rather than to the natural course of the disease?" The answer remains "We do not know."

It is easy to pick out flaws in any method of evaluation of treatment in multiple sclerosis but it is practically impossible to work out a method that considers all the variables and to achieve a scientifically and practically sound approach. Alexander[4] recently reported a scoring system to enable investigators to follow the progress and course of patients with multiple sclerosis. However, this method merely transposes a neurologic status into a number system and does not eliminate any of the fundamental problems involved.

Perhaps the objective neurologic status is not the best means of judging activity in multiple sclerosis. Before the advent of the Wassermann reaction for determining the presence and activity of central nervous system syphilis, the mental and neurologic examinations were the only guides to the course of the disease. Later the Wassermann test, the number of cells, the total protein and the colloidal gold reaction of the cerebrospinal fluid became the criteria for activity in central nervous system lues. However, as is frequently the case, neurologic and mental changes may continue after treatment despite the fact that all the laboratory tests become normal. The direction and character of function of the remaining normal nervous tissue in the presence of many areas of damage is unpredictable. The disease process may become latent and undetectable by laboratory methods.

Nevertheless, it would be a great aid if a laboratory procedure based on a chemical or physiologic function representing an indicator of activity in multiple sclerosis could be developed. Only when we have such a guide will our method of evaluating therapy approach scientific soundness.

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Seminars on Congenital Heart Disease

The Tetralogy of Fallot*

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ASK a group of medical students today about the pathology of the tetralogy of Fallot and almost in unison they will say: stenosis of the pulmonary artery, interventricular septal defect, dextroposition of the aorta and hypertrophy of the right ventricle. The same question put to a group of cardiologists ten years ago would have called forth hesitant mumblings from a few who had taken mild academic interest in the subject. Nothing stimulates greater interest in a disease, hitherto completely hopeless, than the discovery of an effective therapeutic procedure. To Blalock and Taussig goes all credit for the tremendous interest which their operation aroused in the congenital heart deformity known as the tetralogy of Fallot.

Symptoms. Variation in symptoms of the tetralogy of Fallot are wide and more or less proportional to the degree of infundibular or pulmonary stenosis. Frequently the history brings out the fact that cyanosis did not appear until the child was a few months old—obviously due to the fact that the ductus arteriosus remained open for that period of time. Cyanosis may deepen early in life and become extreme or it may be scarcely visible in the lips and finger tips when the child is at rest. Associated with cyanosis there is always an elevation of the red blood cell count. The average red cell count in our patients has been about 7.5 million per cu. mm. A few cases have had counts as high as 12 million with a comparable elevation in the hemoglobin levels.

The child is partially or greatly incapacitated. For some unknown reason children with typical tetralogy of Fallot usually squat when they exceed their capacity for exertion. In fact, it is so commonly reported by parents that squatting when breathless is accepted as a characteristic symptom.

Clubbing of the fingers and toes is usually minimal during the first years of life but becomes more and more pronounced as the child grows up. Suffusion of the sclera and duskiness of the retina are routinely seen in the severely cyanotic.

The child is usually undersize and underweight, is cross, eats poorly and is often badly "spoiled" because the parents would quite justifiably rather accede to the child's slightest whim than have a violent crying spell lead to severe cyanosis and a possible attack of unconsciousness. A murmur, entirely systolic in time, is heard over the left of the sternum and varies from the merest scratch to a harsh, rasping sound. The absence of a murmur in an otherwise typical case is strong evidence of pulmonary atresia. A cyanotic patient with a systolic and a diastolic murmur does not have a typical tetralogy of Fallot.

Roentgenograms of the chest at the usual two meter distance show in typical cases a boot-shaped heart with blunted apex and a concavity in the region of the pulmonary segment. (Fig. 1.) A normal-shaped heart does not preclude a diagnosis of tetralogy of Fallot but enlargement of the heart even to a moderate degree suggests strongly that the case is not typical and in our experience indicates that surgical relief will be impossible or will be followed by an unsatisfactory result. Fluoroscopic examination confirms the roentgen evidence of clear lung fields and demonstrates the absence of hilar pulsations.

The electrocardiogram in a typical case of tetralogy of Fallot shows deviation of the axis to the right. (Fig. 2.) So constant is this finding that justification for surgery in the absence of it must be carefully weighed and then be considered purely as an exploratory procedure.

Such are the findings in a typical case of tetralogy of Fallot, now easily diagnosed by any physician with a modicum of interest in congenital heart disease. Recognition of the atypical but still operable cases, and differentiation of patients with tetralogy of Fallot from those with isolated pulmonary stenosis with intact

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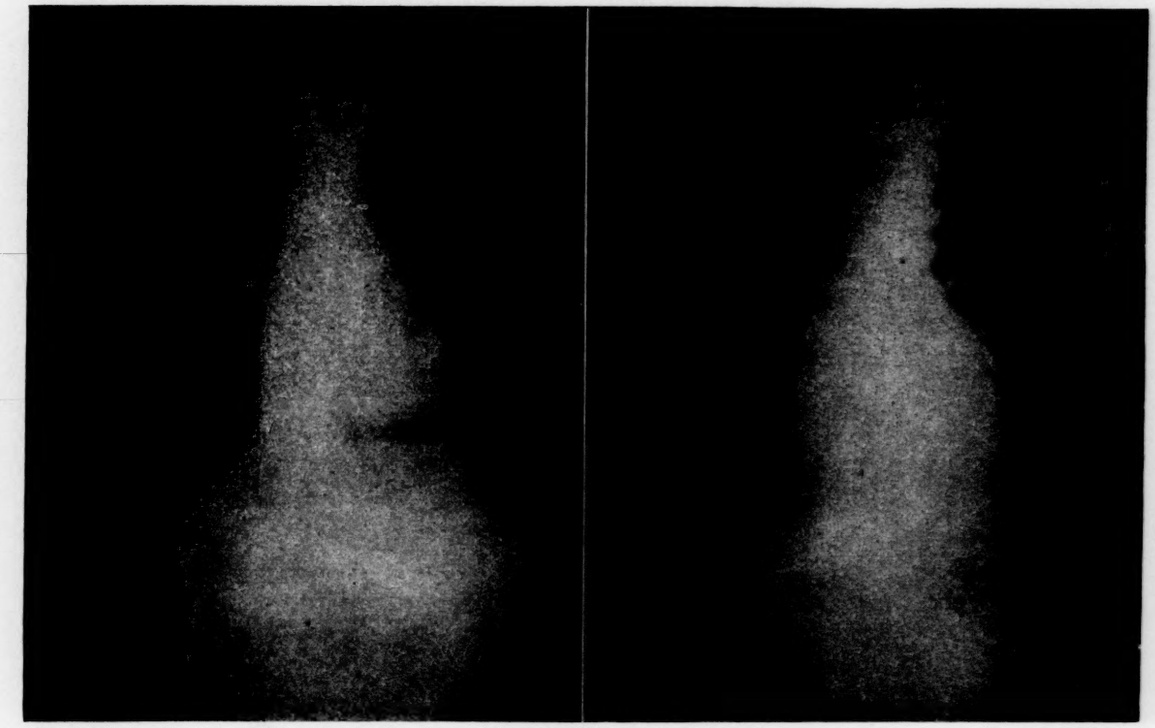

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FIG. 1. A, Typical roentgenogram of a thirteen year old boy with tetralogy of Fallot. Note concavity of the heart shadow in region of the pulmonary segment. The lung fields are clear. B, Two and one-half years after aortic-pulmonary anastomosis. There is some enlargement of the heart and increased vascular markings in the lungs.

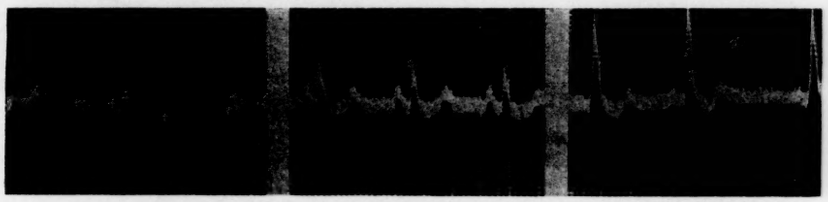

FIG. 2. The electrocardiogram routinely shows right heart strain. The QRS complex is down in lead I and upright in lead III.

interventricular septum require the utmost in diagnostic acumen and demands all the help possible from laboratory and roentgenologic procedures.

Cardiac catheterization and angiographic studies are not only unnecessary but also inadvisable for the average typical case. These procedures and their interpretation require well trained men with specialized skill and should be preserved for unusual and atypical cases. Nothing takes the place of a keen discerning ear and careful interpretation of roentgenograms and electrocardiograms. Angiograms are impressive as "pictures of the inside of the heart" but actually are fleeting shadows which may easily lead one astray.

Indications for Surgery. The assumption that all cyanotic children with congenital heart disease may somehow be benefited by surgery is sadly erroneous. In our experience about 60 per cent of cyanotic children fall into the operable group and 40 per cent have all sorts of anomalies which are remediable by no surgical procedure known to date. If it can be demonstrated that cyanosis is due to diminished blood flow to the lungs, operation is advised regardless of the patient's condition. Not infrequently in an apparently hopeless child, so blue that it cannot live out of an oxygen tent, surgery has been undertaken as a last resort and, I must honestly say to our great surprise, has yielded to us a satisfactory result and to the parents a miracle. In spite of a seemingly unquestionable diagnosis we have found it wise to explain to

the parents before operation that there is always a certain degree of uncertainty about the outcome; the patient may not have a pulmonary artery through which more blood can be shunted to the lungs. The best guide to surgery is skillful diagnosis. This requisite is filled at the Children's Memorial Hospital by Dr. Stanley Gibson.

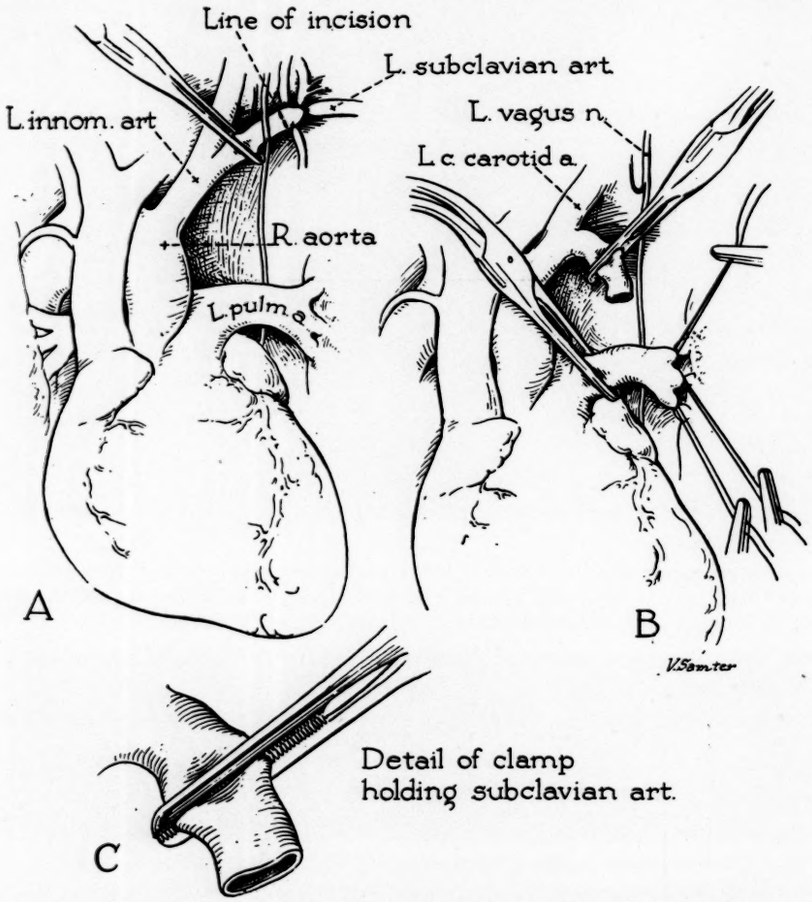

FIG. 3. Subclavian-pulmonary anastomosis is done by occluding the pulmonary artery with one ductus clamp and bringing the proximal end of the subclavian artery down with a second ductus clamp. (From *Ann. Surg.*, 30: 342, 1949.)

The Operation. Blalock and Taussig initiated the surgical treatment of congenital pulmonary stenosis by successfully anastomosing the proximal end of the subclavian artery to a pulmonary artery. Potts, Smith and Gibson reported a method of anastomosing the aorta directly to a pulmonary artery by means of a special clamp. Both operations accomplish the same objective of shunting more blood to the lungs. The choice of either operation is made on the basis of previous experience, the position of the aorta and the age of the patient. If a surgeon has been trained in either the technic of subclavian-pulmonary anastomosis or aortic-pulmonary anastomosis, it is quite natural for him to choose the operation at which he is most skilled. Infants who because of the seriousness of their condition require surgical relief are best treated by aortic-pulmonary anastomosis because the subclavian artery is too small to allow performance of a satisfactory anastomosis which will remain open. (Figs. 3 and 4.)

Because the right pulmonary artery is short and runs at right angles to the aorta, an aortic-pulmonary anastomosis on the right side in patients whose aorta curves to the right is a difficult technical procedure. If there is an advantage in aortic-pulmonary anastomosis, it lies in the fact that the size of the anastomotic channel is controllable.

Our policy in the choice of operation for pulmonary stenosis at present is as follows: The

surgical approach in all children above twelve to eighteen months of age is through the left fourth interspace. If the arch of the aorta curves normally to the left, an aortic-pulmonary anastomosis is done. If the arch of the aorta curves to the right (as it does in approximately 25 per cent of patients with tetralogy of Fallot), a subclavian-pulmonary anastomosis is done on the left. In patients with a right arch the innominate artery is on the left and the subclavian artery is easily drawn down to the left pulmonary artery. In children below one year of age with a right arch the subclavian artery is too small for a satisfactory anastomosis and an aortic-pulmonary anastomosis on the right side will be necessary.

The proper size of the anastomotic channel between the aorta and the pulmonary artery has been much discussed. At present the incisions in the pulmonary artery and in the aorta are made ¼ of an inch (6.3 mm.) long in all cases except in infants, in whom the incisions are made about 1 mm. shorter. Incisions 6.3 mm. long give a completed anastomotic opening 4 mm. in diameter. Such an opening allows sufficient blood to be diverted to the lungs and does not put an undue strain on the heart.

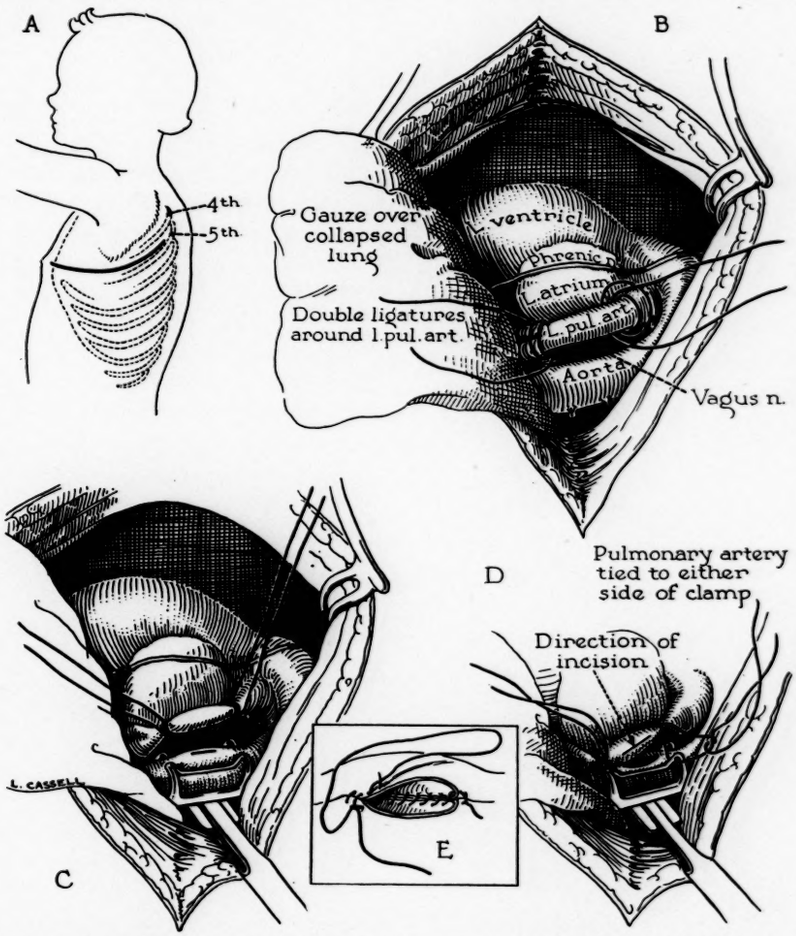

FIG. 4. Various stages of aortic-pulmonary anastomosis. (From *J. A. M. A.*, 132: 627, 1946.)

Brock has approached the problem of surgical relief of cyanosis due to tetralogy of Fallot in a somewhat different fashion. By means of a right transventricular approach he cuts out the stenotic segment in the base of the ventricle with a rongeur. This procedure has merit in that the attack is directly upon the site of the most important pathologic condition—the stenosis. Unfortunately, such surgery at present is a blind procedure and since it requires a rather large incision in the wall of the right ventricle the consequent scar may be the cause

of a future aneurysm. Experience may rectify this but at present the mortality associated with transventricular approach in the tetralogy of Fallot is far higher than that associated with either of the shunt procedures. This method has been advocated in this country by Bailey, Glover and O'Neill. For patients with isolated pulmonary stenosis the Brock procedure of pulmonary valvulotomy yields spectacular results.

Only time, experience and much more experimental work will determine the best operative procedure. Most any day some investigator may come forth with an operation which will supplant all of those being done today.

Anesthesia. Anesthesia for many years was given about as much thought by the surgeon as preparation and draping of the patient's abdomen. So long as the patient lay still and the abdominal muscles were relaxed the surgeon was happy. During the past few decades the need of skilled anesthesia for preventing unnecessary deaths has been established by pioneers in this field. In cardiac surgery in general, but especially in the surgery for pulmonary stenosis, the need of services of an expert anesthesiologist is being recognized. To pour ether on a mask for an operation for inguinal hernia is one thing but to carry a patient critically ill with severe cyanosis through a two-hour operation is quite another. Operative mortality will in a measure be proportional to the skill of the anesthesiologist.

Preoperative medication for children as well as for adults is best accomplished with morphine in liberal doses, well balanced with atropine or scopolamine. For example, a five-year old child receives $\frac{1}{8}$ gr. (8 mg.) of morphine sulfate and $\frac{1}{200}$ gr. (0.3 mg.) of scopolamine hydrobromide one hour before operation. Blind adherence to Young's rule has long been a handicap in prescribing preoperative morphine for children. The child should come to the operating room drowsy and indifferent to its surroundings. This entire article could profitably be a dissertation on the importance of prevention of psychic trauma to children going to an operating room.

The child is anesthetized with ether, is intubated and then carried through the operation on cyclopropane given in such amounts that the child is unconscious but in the first plane of anesthesia. Complete relaxation is unnecessary when making an incision through the chest wall. Contrary to many reports we have not had cardiac irregularities as a result of anesthesia with cyclopropane. The patient's greatest need in any operation is oxygen and more oxygen. Dr. William O. McQuiston, Director of our Anesthesia Department, says, "If you don't know what to do in any emergency, give oxygen and you'll be right 90 per cent of the time."

Simplicity in anesthesia as in any other phase of medicine is still important. Detection and interpretation of the slightest variation from normal respiration or cardiac action of the anesthetized patient followed by prompt correction is the secret of low anesthetic mortality. If a patient has had nembutal, morphine and atropine before operation, and during operation receives intravenous pentothal in one vein, novocain in another, is breathing a mixture of nitrous oxide, ether and oxygen, and then is given a shot of curare, how can any anesthetist know what to do for an emergency that suddenly arises? Simplicity and moment-to-moment control of exchange of gases are of the greatest importance in the following subject of discussion.

Cardiac Arrest. Cardiac arrest or standstill is properly defined as sudden, unexpected cessation of heart action during an operation on a patient who does not have a demonstrable pathologic condition to explain the catastrophe. This term has been used freely of late and at times one suspects it to be a convenient phrase to explain sudden death during surgery.

It is extremely unusual to have a healthy person with a normal heart drop dead because of cardiac arrest. It just does not happen. Why should such a person die of cardiac arrest during operation? The reason for such misfortune will be considered. It must be remembered that if a heart stops during operation and at postmortem examination occlusion of the coronary artery or fresh hemorrhage in the brain, etc., is found, the patient did not die of what is commonly called cardiac arrest. Furthermore, if during operation hemorrhage has been severe and blood has not been replaced, death cannot be blamed on a heart that has ceased to function.

The causes of cardiac arrest are being recognized primarily as due to poisoning by the anesthetic agent or agents, inadequate exchange of gases or a combination of both. Oxygen is important for life every moment. The conscious person can make known his need for oxygen but the deeply unconscious person can only feebly, or not at all, signal his need of oxygen. The heart is extremely depend-

ent upon a continuous supply of oxygen; and if it is temporarily deprived or even partially deprived of fuel for a sufficiently long period of time, the heart stops. A plug of mucus, a mess of vomitus or a clot of blood in the patient's trachea during operation interferes with the normal exchange of gases. Consequent hypoxia results in cardiac arrest but not the cardiac arrest under discussion. Such a patient's heart stops because of suffocation.

The following statement is an extremely dangerous one to make because Solomon long ago said, "Pride goeth before destruction and an haughty spirit before a fall." If cardiac arrest is defined as unexplained cessation of heart activity without demonstrable cause, we have had but one questionable case in over 700 heart and lung operations during the past five years in children up to age sixteen years, and none in many more minor and major operations routine to pediatric surgery. Tomorrow I may regret having made this statement. What is the reason for this good fortune? Certainly not because our surgery differs from that done in a thousand other hospitals. I believe credit should go entirely to the department of anesthesia because of their constant attention to the depth of anesthesia—heart and lung cases are carried in the first plane—and to meticulous and zealous insistence that the airway be unobstructed and that adequate exchange of gases take place.

If in spite of the utmost care, skill, diligence and judgment cardiac arrest does occur, prompt rhythmic massage of the heart is imperative. After a few minutes of massage an intracardiac injection of adrenalin may be effective in restoring normal contractions. How long massage should be continued is an unanswerable question. The brain is extremely sensitive to anoxia and some things are worse than death.

Temperature Control during Operation. For years it has been customary to keep the temperature in operating rooms above the usual 72°F. Why? Because of a long revered but false notion that the patient might catch pneumonia. The warm room, heavy drapes and hot lights make every patient's temperature go up during a long operation.

Oxygen consumption increases 7 per cent with each degree elevation of temperature. There is obviously, therefore, a sizeable difference in the amount of oxygen consumed by a patient whose temperature is 95°F. and by one whose temperature is 103°F. Since hypoxia is the prime danger during surgery for pulmonary stenosis and since insufficient blood is flowing to the lungs to pick up the available oxygen, it is of the greatest importance to conserve the oxygen the patient is capable of absorbing.* Patients with pulmonary stenosis have a greater tendency toward temperature elevation during operation than other patients. Often the temperature rises to 102° and 103°F. within the first hour of anesthesia. The more cyanotic the patient the more the temperature tends to go up.

It is now our custom to reduce the temperature of the severely cyanotic patients to 96° or 97°F. by beginning a flow of cold water through the mattress as soon as the patient is anesthetized. When the temperature has been reduced to the desired level, the water is warmed a bit or the temperature will continue to fall. One infant's temperature fell to 92°F. during surgery without later ill effects. We have seen no increase in postoperative complications since we adopted this plan and furthermore we have not had a death from anoxia on the table in approximately 200 cases, whereas we had had two such deaths in one-half that number before we adopted routine temperature control.

We now employ temperature control in all major surgery. If the patient's temperature goes up, cool water is run through the mattress; if the temperature is subnormal, as is not uncommon in severely ill infants, warm water is circulated. Some years ago a long operative procedure on a very hot summer day on a child with syndactylism terminated fatally from hyperthermia the night after surgery. The death was unnecessary.

Mortality. Any dissertation on mortality statistics is apt to be misleading because of various methods of grouping cases according to severity, age, etc. In our experience there has been a rather definite dividing line between the high and low mortality groups on the basis of age. During the first three years of life and especially during the first year of life the mortality in the surgery for tetralogy of Fallot is high. The reason for this is actually not the child's age at all but the fact that these little

* Dr. John A. Bigler had the Central Scientific Company build a thermo-electric thermometer with a thermocouple for insertion into the rectum; and the Davol Rubber Company manufacture a rubber water mattress for the operating table for temperature control. For the past three and one-half years we have routinely used this equipment for the control of temperature during heart surgery.

children are severely afflicted and are operated upon as desperation cases only because life is impossible without surgical relief. If the child has sufficient blood flow to the lungs to survive to three years of age, its chances of recovery are good, not because he has reached the magic age of three years but because his condition was never such that emergency surgery was necessary earlier.

In the group of 117 patients between the ages of eleven days and three years there have been twenty-six deaths or a mortality of 22 per cent. Compare these figures with the group of 166 children operated upon between the ages of three and sixteen years with four deaths, or a mortality of 2.4 per cent. In other words, if the child's condition is such that it can carry on to three years of age, its chances of surviving a shunt operation for the relief of cyanosis due to tetralogy of Fallot is about 97 per cent.

Results. The results in those patients who have survived aortic-pulmonary or subclavian-pulmonary anastomosis have been satisfactory to us, spectacular to the parents and acceptable to the children. We are keenly aware that the pathologic condition inside the heart has not been corrected and that the surgical procedure has added an extra burden on the heart muscle. The parents see only the change in color, the increased appetite and are grateful for the relief from the anguish of being unable to do anything for their unhappy child. The youngster nonchalantly accepts its new lease on life, runs and plays blissfully unmindful of any need for protecting his heart muscle.

Dr. C. E. Leininger last year made a follow-up study of 145 patients upon whom a successful anastomosis had been performed from six months to forty-two months previously. Eight of these children died after the operation; two from pulmonary stenosis and previously unrecognized transposition of the great vessels, one from rupture of a small aneurysm in the lung, one of a brain abscess, one of an automobile accident, one following an ill advised extensive operation for bilateral hernias and undescended testicle, two of heart failure and one of causes unknown.

Five of the remaining children have marked enlargement of the heart and will undoubtedly go into eventual heart failure. There is some enlargement of the heart in every case following a shunt operation. Within a relatively short time, usually a month or two, the maximum enlargement of the heart has occurred. After that, as the child grows the cardiothoracic ratio remains relatively fixed. It is impossible to predict before or immediately after operation which children are going to get along well. In general, older children get along better over a period of years than the children who have been operated upon during the first three years of life.

What the prognosis for life may be no one can yet hazard a guess. Certainly the life expectancy of these patients will be well below normal. However, as time goes by these children grow up, get married, have children and, with restrictions, enjoy life. For psychic reasons little children are not restricted in their activities but as soon as they become old enough to understand reasoning they are told that they have a permanent handicap and that they will have to be considerate of their heart muscle. Competitive athletics are absolutely forbidden.

In conclusion, shunting blood to the lungs for the relief of cyanosis due to tetralogy of Fallot is a far from perfect but a satisfactory operation. The operative mortality is not too great and the results thus far warrant its continued use until a better operation is devised.

Research Society Abstracts

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE MIDWESTERN SECTIONAL MEETING IN CHICAGO, ILLINOIS, NOVEMBER 1, 1951

EFFECTS OF ALTITUDE STRESS ON THE HUMAN CIRCULATORY SYSTEM. *Sanford A. Franzblau, M.D., Gordon F. Vawter, M.D. (by invitation); Clarence V. Pestel, M.D. (by invitation) and John P. Marbarger, M.D., Ph.D. (by invitation).* (From the University of Illinois, Chicago, Ill.)

Observations are reported on ten normal young adult males taken to simulated altitudes of 10,000 and 18,000 feet in an air-conditioned, low-pressure chamber while resting on a horizontal, low-frequency, critically damped ballistocardiograph: arterial blood oxygen, carbon dioxide and cellular components, simultaneous electrocardiogram, ballistocardiogram, direct arterial and venous blood pressure readings, respiratory rate, depth and the composition of alveolar air were determined. Analysis of the records appears to justify these conclusions: Total effective peripheral resistance to blood flow decreases markedly upon exposure to ambient atmosphere at simulated altitudes up to 18,000 feet. "Useful work of the left ventricle" is not significantly altered after ten minutes exposure to ambient atmosphere at a simulated altitude of 10,000 feet but is increased by approximately 50 per cent after as short an exposure as five minutes to an altitude of 18,000 feet. The administration of "100 per cent oxygen" at a simulated altitude of 18,000 feet causes an almost immediate return of these measurements to ground-level values. Sudden exposure to the inhalation of ambient air at 18,000 feet increases both the pulse rate and stroke volume. The pulse rate reaches its maximum value within ten minutes. The stroke volume continues to increase as the time of exposure continues (up to twenty minutes). Increased stroke volume plays an important role in increasing cardiac output at high altitudes, especially noteworthy when cardiac output is increased to more than 50 per cent above the ground-level value.

OBSERVATIONS ON THE ERYTHROCYTE SEDIMENTATION RATE IN CONGESTIVE HEART FAILURE. *Albert E. McGinnis, A.B. (by invitation), W. Edward Lansche, A.B. (by invitation) and Robert J. Glaser, M.D.* (From the Department of Internal Medicine and the Oscar Johnson Institute for Medical Research, Washington University School of Medicine, St. Louis City Hospital and the Barnes Hospital, St. Louis, Mo.)

Evidence supporting the rather widely held dictum that the erythrocyte sedimentation rate (ESR) is normal in congestive heart failure is limited. In order to elucidate this particular point, the ESR was determined serially for forty-eight patients during fifty-one separate bouts of congestive heart failure. Of these, thirty-eight were acute episodes from which the patients recovered, six were classified chronic because the patients failed to regain compensation and seven terminated fatally. None of the patients exhibited demonstrable evidence of other complications such as myocardial or pulmonary infarction, thrombophlebitis, infection, pregnancy or other conditions known to lead to elevation of the ESR.

In acute congestive heart failure (thirty-eight instances), the ESR was normal in twelve (31.5 per cent) and elevated in twenty-six (68.5 per cent); after recovery the respective values were four (10.5 per cent) and thirty-four (89.5 per cent). The ESR in chronic intractable failure (six instances) was normal in one patient and elevated in five, not only on admission but throughout the hospital stay. In the seven cases in which congestive failure was fatal, four of the patients had a normal ESR on entry; terminally, the ESR was normal in five and elevated in two.

These results suggest that the ESR is usually not normal in either acute or chronic congestive heart failure. The ESR is therefore of little value in confirming the presence or absence of any of the several complications which occur commonly in patients suffering from cardiac decompensation.

ANALYSIS OF THE IMPORTANCE OF ANTITHROMBIN IN THROMBOEMBOLISM. *T. D. Pemrick, M.D. and M. M. Musselman, M.D.* (From the

Department of Surgery, Wayne County General Hospital, Eloise, Mich.)

Several investigators have reported finding a decrease in antithrombin in patients with diseases which predispose to thromboembolism. The recent work of Seegers on the nature of these antithrombin substances challenges the validity of the methods of measurement used by these investigators.

Using the Seegers test which is believed to be a true test for antithrombin, we have determined levels of antithrombin in patients with diseases most commonly complicated by thromboembolism. In most there was no change and in none were the levels lowered.

In nine postoperative patients the level of antithrombin did not fall. The level was elevated in all by the second postoperative day and remained elevated for fifteen to seventeen days when antithrombic activity gradually returned to normal.

Since heparin co-factor may act as antithrombin or antiprothrombin, we determined its antithrombic activity in the same type of patients. In patients with diseases of the liver, carcinoma of the pancreas, pulmonary infarction, coronary thrombosis and thrombophlebitis the level was increased. In the postoperative patients there was an elevation immediately after operation which persisted for from four to six days, gradually returning to normal. Levels below normal were never found.

TIME RELATIONSHIP FOR THE SHIFTS IN NEUROGENIC AND HUMORAL CONTROL OF BLOOD PRESSURE DURING NORMAL AND TOXEMIC PREGNANCIES. *N. S. Assali, M.D., J. M. Vergon, M.D. (by invitation), Y. Tada, M.D. (by invitation) and J. G. Rosenkrantz, M.D. (by invitation), Cincinnati, Ohio.*

Because of increased neurogenic tone, normal pregnant women at term respond to TEAC with marked fall in blood pressure. This fall is not seen in toxemia of pregnancy because the blood pressure is maintained possibly by humoral mechanisms.

This study was undertaken to investigate at what period of gestation the shift to neurogenic or to humoral control of blood pressure occurs. Twenty normotensive pregnant subjects were given TEAC tests biweekly during the entire prenatal course and two to ten days after delivery. In the fourteen patients who remained normotensive and free of toxemia, the following responses were observed: (1) negligible blood pressure fall up to the fifteenth week; (2) thereafter, a progressive fall reaching its maximum at term, averaging 40 per cent of the control blood pressure; (3) this fall could be prevented by "excluding" the legs from the body by cuffs.

The six patients who developed toxemia during the last trimester showed the following responses: (1) negligible fall up to the sixteenth week; (2) a fall parallel to the normotensive group up to the twentieth week; (3) a progressive rise reaching its maximum near term when the symptoms of toxemia were prominent; (4) the rise in TEAC "floor" preceded any other sign of toxemia.

The data suggest that the increase in neurogenic tone to the vascular bed in normal pregnancy occurs around the fifteenth week of gestation; the shift to humoral maintenance of blood pressure in toxemia occurs around the twenty-second week of gestation and becomes evident before any other clinical signs; the TEAC test might be a valuable screening method in the diagnosis of toxemia of pregnancy.

EXPERIENCES WITH MITRAL VALVE SURGERY. *Forrester Raine, M.D. (by invitation), Henry F. Twelmeyer, M.D. (by invitation), Timothy R. Murphy, M.D. (by invitation), Paul G. LaBissoniere, M.D. (by invitation), Armin R. Baier, M.D. (by invitation), Nathan Grossman, M.D. and Howard L. Correll, M.D. (by invitation), Milwaukee, Wis.*

To date nineteen cases of mitral valvular disease have been catheterized. The clinical differentiation of the predominance of mitral stenosis or mitral insufficiency by means of murmurs has been of little value. Pulmonary hypertension is not diagnostic and the degree of pulmonary hypertension is not correlated with the size of the chambers of the heart as seen at surgery. Pulmonary capillary pressure tracings are helpful but technically difficult to obtain. There is also the danger of pulmonary infarction if the catheter is left in place an appreciable length of time.

Ten cases were candidates for surgery. One was operated upon elsewhere and nine by this group. One patient proved by exploration to have marked insufficiency with minimal stenosis. In eight cases the mitral valves were successfully operated upon. Calcified valves have proven to be more readily and more satisfactorily enlarged by surgery.

Cerebral emboli with non-disabling residuals have occurred in two cases. One patient, oper-

ated upon within two weeks following catheterization, developed a questionable subacute bacterial endocarditis. The nine patients successfully operated upon have been remarkably improved from the standpoint of orthopnea, exercise tolerance, need for diuretics and general well being. There has been little demonstrable change in the murmurs heard postoperatively or in the heart size.

THE PHYSIOPATHOLOGY AND THE THERAPEUTIC PROBLEM IN ASYMPTOMATIC MASSIVE HEMOPERICARDIUM WITH PARTIAL CARDIAC TAMPONADE. *William H. Ames, M.D. (by invitation), James W. Culbertson, M.D., Ernest O. Theilen, M.D. (by invitation), Rodman E. Taber, M.D. (by invitation), James G. Easton, B.A. (by invitation), and Steven M. Horvath, Ph.D. (by invitation), Iowa City, Iowa.*

Acute hemopericardium with dramatic cardiac tamponade is well known clinically and experimentally. Chronic hemopericardium occupies an intermediate hemodynamic position between this and chronic constrictive pericarditis and may be asymptomatic. Such a case, presumably traumatic, was discovered accidentally and studied carefully by clinical and cardiac catheterization methods.

Physical, electrocardiographic, radiographic and roentgenkymographic findings suggested pericardial effusion. Venous pressure was 170 mm. saline and decholin circulation time eighteen seconds. Elevated pressures were recorded in mm. Hg as follows: right atrium 20/15, right ventricle 32/12, pulmonary artery 31/16 and pulmonary "capillary" 12 (mean). Resting minute volume cardiac output was a normal 6.4 L./min. During exercise this rose to only 6.6, while stroke volume declined abnormally from 70 to 57 ml. Aspiration of 380 ml. of unclotted blood (shown by chemical and hematologic studies to be old and disintegrating) from the pericardial space caused a decline of intrapericardial and right atrial pressures toward normal.

At subsequent elective thoracotomy and partial pericardiectomy 500 ml. of additional old pericardial blood was removed. Sections of excised pericardium showed an inflammatory and fibroblastic reaction, suggesting the process might have progressed to constrictive pericarditis if treated conservatively.

Cardiac catheterization three and one-half weeks postoperatively revealed essentially normal resting values throughout. A recent leg injury prevented repetition of the exercise test, so that cardiac reserve response remains to be measured in this patient. Moreover, the general problem of conservative versus surgical therapy in such cases deserves further investigation.

NATURE OF THE IMMEDIATE PHYSIOLOGIC ADJUSTMENT TO THORACIC SURGERY. *William W. Stead, M.D., Minneapolis, Minn.*

Physiologic studies were performed in ten patients preoperatively and sixteen to twenty hours after each of three stages of thoracoplasty to define the nature of the problems encountered.

The mean fall in hemoglobin saturation was mild (95.7 per cent preoperatively and 90.7 per cent postoperatively), and could largely be accounted for by the presence of a 15.3 per cent shunt of blood through recently collapsed lung tissue. The arterial blood pH (7.40), carbon dioxide content (21.36 mm./L.) and P_{CO_2} (39 mm. Hg) remained unchanged.

The mean rate of carbon dioxide elimination rose from 217 to 230 cc. per minute. The volume of ventilation rose from 6,180 to 7,234 cc. per minute. This was accomplished purely by an increased respiratory rate (from 14.5 to 19.6) which, coupled with a rise in physiologic dead space (from 143 to 154 cc.), resulted in a mean increase of 58 per cent in dead space ventilation (2,057 to 2,978 cc. per minute). Tidal volume fell from 430 to 390 cc. and tidal alveolar ventilation from 241 to 192 cc.

The inefficiency of the respiratory mechanism immediately following thoracic surgery is clearly shown. A greater alveolar ventilation is most efficiently accomplished by increasing the tidal volume. However, when the tidal volume is limited by pain and paradoxical chest motion. any need for an increase in alveolar ventilation must be met by more rapid (shallow) respirations.

When a patient does poorly following thoracic surgery, a diagnosis of respiratory acidosis should be considered along with the other possibilities. Rational therapeutic measures to aid in the elimination of carbon dioxide will be discussed.

GENTISIC ACID AND DERIVATIVES IN THE TREATMENT OF RHEUMATIC FEVER. *Norman E. Clarke, M.D. (by invitation) and Robert E. Mosher, Ph.D.* (From the Department of Research, Providence Hospital, Detroit, Mich.)

Gentisate gave prompt relief in all forms of rheumatic fever with slight or no toxic reactions in seventy-five patients. Disadvantages of gentisate are rapid excretion and poorly sustained blood levels requiring frequent administration.

We have compared the chemistry and therapeutic value of gentisic acid and several derivatives in twenty-seven patients. Gentisic acid and sodium gentisate are 50 to 70 per cent excreted and the ethanolamide of gentisic acid only 20 to 30 per cent in twenty-four hours. Blood levels of different compounds were not uniform with the same clinical response. The ethanolamide showed lower blood concentrations, probably due to more uniform dispersion throughout the body fluids, it was not excreted in the stool and did increase total ethereal sulfate and glucuronic acid output several times more than did gentisic acid, sodium gentisate or salicylates.

Caronamide did not reduce gentisate excretion; benemid did in children but increased excretion in adults. An absorption complex of gentisic acid and a polyamine resin behaved like gentisic acid. A mixture of sodium gentisate and methyl cellulose retarded absorption from the bowel and gave lower but sustained blood levels but did not retard excretion.

Compounds showing specific antirheumatic activity are aromatic acids with phenolic groups in particular positions or can be metabolized to such compounds. Examples are salicylic acid, amatin, cresotinic acid, gentisic acid and gamma resorcylic acid. Other related compounds may be therapeutically superior to those mentioned.

TREATMENT OF ACUTE RHEUMATIC FEVER WITH ASPIRIN, HPC, CORTISONE OR ACTH. *Capt. Ernest J. Clark, M.C., USAF and Maj. Harold B. Houser, M.C., USAF (introduced by Charles H. Rammelkamp, Jr., M.D.)* (From the Medical Service and the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, Wyo.)

As part of a cooperative project of the American Council on Rheumatic Fever, the comparative effects of aspirin, 3-hydroxy 2-phenyl cinchoninic acid (HPC), cortisone and ACTH on the clinical course of acute rheumatic fever and the incidence of subsequent heart disease were studied. Diagnostic criteria for admission to the study and selection of the patients for the treatment groups were determined in a standard manner.

There were 104 consecutive young adult airmen with rheumatic fever of which seventeen received ACTH, seventeen cortisone, thirty-four HPC and thirty-six aspirin. Treatment was administered for a six-week period. Observations were made daily for the first nine weeks and at monthly intervals thereafter.

All four drugs employed appeared to be effective in relieving symptoms. Arthritis subsided most rapidly in the group receiving aspirin; ACTH and cortisone were more effective than HPC. There was no significant difference in the duration of fever or A-V block in any of the four treatment groups.

Following treatment with ACTH or cortisone the majority of patients had a return of one or more signs of rheumatic activity. These usually occurred early, were mild, of short duration and did not require retreatment. Approximately one-half of the patients treated with aspirin or HPC had a recurrence of activity which was usually moderately severe; however, only two patients required retreatment.

The effect of these four compounds on carditis as determined by four months of observation on seventy patients will be presented.

EFFECTS AND CLINICAL SIGNIFICANCE OF BACTERIAL CONTAMINANTS IN TRANSFUSED BLOOD. *A. I. Braude, M.D., Jay P. Sanford, M.D. (by invitation), Jane E. Bartlett, B.S. (by invitation) and O. T. Mallery, Jr., M.D., Ann Arbor, Mich.*

Bacterial contaminants were isolated from 38 (2.24 per cent) of 1,697 consecutive pints of bank blood. Despite this relatively high rate of contamination, only one transfusion reaction could be definitely traced to growth of bacteria in this group of contaminated bloods.

The infrequency of reaction from contaminated bloods was explained by the growth curves of 93 organisms and bactericidal action of 162 bloods. The following factors protect the recipient from heavy growth: (1) bactericidal or growth-suppressive action of blood at both room temperature and in the refrigerator (most bloods retained bactericidal power while refrigerated for at least seven weeks; in a few this was lost and heavy growth developed subsequently at 4°C.); (2) long lag phase preceding multiplication of organisms in blood not possessing bactericidal or suppressive properties; (3) small number of bacteria per ml. of contaminated blood.

The effects of heavy growth in human blood are marked hemolysis, increased erythrocyte fragility and clotting due to consumption of citrate caused by numerous strains of bacterial contaminants. Blood type, however, was altered only once in 113 contaminated specimens. Rabbits transfused with blood containing a heavy growth of staphylococci, the commonest contaminant, experienced fever but no serious

harm. By comparison, A. aerogenes was usually lethal.

These harmful effects probably occur clinically under conditions which permit sufficient incubation of large inoculums in transfused blood at room temperature or under refrigeration.

IMPROVED METHOD OF CALCULATING LONGEVITY IN MALIGNANT CONDITIONS. *William R. Best, M.D. and Louis R. Limarzi, M.D. (by invitation)*. (From the University of Illinois, College of Medicine, Chicago, Ill.)

The characteristic duration of illness from first symptom to death in various malignant conditions is not accurately represented by mean longevity. In each large series a few patients will live much longer than is usual, inordinately influencing the calculated mean. Reports frequently originate from active services in which many patients may yet be alive. Their inclusion in the analysis may make longevity appear shorter than actual as their disease is still in its course; their exclusion would often rob the statistics of cases with unusually long survival. A method of accumulative analysis on a logarithmic time scale is presented, to incorporate incomplete and unusual data in the statistics at the same time giving a true representation of longevity trends. Percentage survival in each longevity interval is calculated, not on the basis of all cases studied, but on the basis of all cases known dead plus those alive and surviving at least to the lower limits of that interval. When plotted on semi-logarithmic paper, longevity times may be determined for any given percentage of survival. Of most interest is the 50 per cent survival time; 90 per cent and 10 per cent intervals will indicate the usual spread of longevity. From the same graph the percentage of subjects surviving arbitrary times limits such as one-half, one, or five years may be determined. These technics have been applied with profit to 370 cases of leukemia observed over the past fifteen years, as well as to other studies reported in the literature.

STUDIES IN THE REACTION TO THERAPEUTIC IRRADIATION: I. BLOOD PICTURE AND COAGULATION MECHANISM. *Harry E. Ezell, M.D. (by invitation) and Allan C. Barnes, M.D.* (From the Department of Obstetrics and Gynecology, Ohio State University College of Medicine, Columbus, Ohio.)

In recent years there has been an increasing consideration of the post-irradiation syndrome with particular emphasis on the resulting hemorrhagic tendencies. These studies have in general depended entirely on animal experimentation, and have been concerned with total body irradiation.

The present study was undertaken to determine whether the phenomenon observed in the laboratory animals exposed to lethal dosages of irradiation could be detected in patients receiving therapeutic irradiation. On women receiving radiation for cervical carcinoma, the following studies were performed: protamine titration, bleeding and clotting times, complete blood counts, hematocrit determinations, total proteins, A/G ratio, blood viscosity and prothrombin level. In each instance the studies were started at the beginning of external x-ray therapy, were followed during treatment with radioactive cobalt and/or radium, and have been continued throughout the period of greatest clinical morbidity.

The findings to date indicate some deviation from normal in the coagulation mechanism, but the patient under a therapeutic regimen of irradiation does not develop the same pattern of changes seen in the animal exposed to flash irradiation. The deviations encountered in blood viscosity have not been reported previously. The significance of these changes as they relate to patient response to roentgen therapy is discussed.

LYMPHATIC DRAINAGE OF SILVER-COATED RADIOACTIVE METALLIC GOLD COLLOIDS FOLLOWING INTRAPULMONARY ADMINISTRATION. *P. F. Hahn, Ph.D.* (From the Cancer Research Laboratories, Meharry Medical College, Nashville, Tenn.)

Previously it has been pointed out that when radioactive colloidal gold is administered by the intrapulmonary route the material remains largely in the lung parenchyma. Drainage by lymphatics in that area is so slow as to prevent adequate radiation of the lymph nodes in metastatic processes associated with bronchogenic tumor. Recent studies with Ag^{111} colloids show prompt drainage by the lymphatics of the lung. Technical difficulties in this isotope's production make it unlikely that the silver colloid shall soon be used therapeutically. Using radio colloidal metallic gold particles as nuclei and coating these with silver, it was found that the body's reaction was the same as toward the metallic silver colloids. Within two days the tracheal bifurcation lymph nodes had picked up 22 per cent as much material as was

resident in the lobe of the instilled lung. At five days tracheal and mediastinal nodes had actively participated, and by the end of ten days all nodes in this region had concentrations of the radioactive material of the order of from one-half to three times the concentrations of the lung.

Therapeutic implications in primary lung and bronchogenic tumors are obvious. Parenchymal tissue can be irradiated by instillation of gold colloid and the metastatic processes in the lymphatics treated by the silver coated gold colloid. Studies are underway in which the silver coating is also radioactive, enabling one to differentiate between the fate of the radioactive gold nucleus and the silver coat.

METABOLISM OF GLYCINE 2-C^{14} IN MAN: THE TISSUE DISTRIBUTION AND URINARY EXCRETION OF C^{14}. *N. I. Berlin, M.D., B. M. Tolbert, Ph.D. (by invitation), H. C. Lee, B.S. (by invitation) and C. Lotz, M.A. (by invitation), Berkeley, Calif.*

In a previous communication it was shown that approximately 86 per cent of the C^{14} administered as glycine 2-C^{14} was excreted via the lungs. This communication reports the urinary C^{14} excretion and the data from post-mortem studies.

The volume of each spontaneous urinary voiding was noted, and an aliquot dried in vacuo and combusted to CO_2, the specific activity measured either by proportional counting or in an ionization chamber. The urinary C^{14} excretion may be described in terms of three rate components having average half times of one-fourth, two and fifty days. The total C^{14} output in the urine is approximately 12 per cent of the administered quantity.

Data on patients autopsied at 56, 106, 165 and 526 days showed a progressive decrease in the amount of C^{14} present in the tissues. In the first three patients the half-time for this decrease was approximately fifty days. The C^{14} levels at 526 days were higher than anticipated by extrapolation from the first three patients, thus indicating an additional slower component of elimination of C^{14} from the tissues.

In general there was no great variation in the amount of C^{14} present in the different tissues with the exception of fat, in which it was consistently low. Bone had a specific activity about mid-way between the extremes.

This makes possible complete accountability for the administered C^{14}; 86 per cent excreted in the breath, 12 per cent in the urine, and 2 per cent too slowly to measure with currently available instruments, but nevertheless slowly eliminated.

EFFECT OF EARLY SMALL EXCHANGE TRANSFUSION ON THE X-IRRADIATED DOG. *Scott N. Swisher, M.D. and Frank W. Furth, M.D. (introduced by Lawrence E. Young, M.D.)* (From the Department of Medicine and the Atomic Energy Project of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.)

It has recently been demonstrated that mortality from ionizing radiation exposure can be influenced in a number of ways in various species. In the present experiment twenty dogs were exposed in pairs to 550 r. of x-radiation (expected LD 80) immediately following which one dog of each pair was rapidly bled 250 cc. and transfused an equal amount of fresh citrated (acid-citrate-dextrose solution) compatible dog blood. Control dogs were untreated. Typical changes induced by ionizing radiation exposure appeared equally in the peripheral blood of the two groups. Sixty per cent of the untransfused dogs died from the fourteenth to eighteenth days. One died on the thirty-eighth day. Forty per cent of the dogs given small immediate exchange transfusions died from the twenty-first to twenty-seventh days. The difference in ultimate mortality in the two groups is statistically of a low level of reliability due to the small number of animals involved. However, the marked delay in onset of morbidity and mortality in the transfused group appears to be very significant. In this laboratory with large numbers of similar groups of irradiated untreated dogs, a delay in onset of mortality to the twenty-first day post-radiation has never been encountered.

This observation may be related to those of other investigators who have found decreases in mortality in x-irradiated animals induced by shielding various organs or parts of the animal during exposure, by implanting fresh splenic tissue surgically shortly after irradiation, or by establishing parabiosis or cross-transfusion closely following x-radiation injury.

THERAPY OF MALIGNANT DISEASES WITH PROTEINIMINE. *M. J. Brennan, M.D., R. W. Monto, M.D., G. H. Mangun, Ph.D. and F. W. Hartman, M.D., Detroit, Mich.*

Under certain conditions methyl-bis-(beta-chloroethyl)-amine couples with plasma proteins to form products having radioimetric activity.

Kelly, Mangun, Sanders and Hartman have described these agents and have labelled them collectively as proteinimine.

Fifty-nine patients have been given a total of more than 600 doses of proteinimine. Ninety-seven and eight-tenths per cent injections were given without symptoms other than mild anorexia. Neither agranulocytosis nor severe thrombocytopenia were encountered.

Clinical improvement was obtained on one or more occasions in seven of twelve cases of Hodgkin's disease, eight of whom were far advanced. Favorable clinical responses occurred in three of four cases of lymphosarcoma; two of seven cases of acute lymphatic leukemia; and two of four cases of acute monocytic leukemia. Repeated remissions occurred in one of two cases of lymphoepithelioma. One case each of Ewing's sarcoma, neuroblastoma, hemangiosarcoma and embroyonal-cell carcinoma responded well to therapy. Remissions were induced in two cases of polyarteritis and one of two cases of acute disseminated lupus erythematosis. There was no improvement in one case of acute myelogenous leukemia, one of chorioepithelioma and two of multiple myeloma. Transient symptomatic benefit was observed in four of thirteen cases of metastatic carcinoma.

The authors believe that the results of treatment are comparable to those available with nitrogen mustard. Advantages of proteinimine are: (1) virtual absence of nausea and vomiting and reduced hematopoietic toxicity, (2) ability of children and adults with acute leukemia to tolerate treatment and (3) suitability for use in outpatients.

STUDIES ON THE LEUKOCYTIC CHANGES DURING THE TUBERCULIN REACTION. *Noreen G. Brandt, Ph.D. and Jorgen M. Birkeland, Ph.D. (introduced by Claude-Starr Wright, M.D.), Columbus, Ohio.*

A study in fifty-two tuberculous and twenty normal rabbits showed that the intravenous and intracutaneous injection of P.P.D. into the tuberculous rabbits results in a 70 per cent decrease in the absolute number of circulating lymphocytes. Normal rabbits had only a slight decrease. This lymphocytic decrease was progressive beginning in one hour and reached a maximum in six to nine hours after which the count returned to normal. The reaction was independent of the diurnal variation. This lymphocytic reaction of tuberculous rabbits to P.P.D. resembles that observed by White and Dougherty following the injection of adrenal cortical hormones into normal animals. However, no evidence was obtained to indicate that adrenal cortical stimulation was the mechanism of the lymphocytic decrease during the tuberculin reaction. It is thought that the lymphocytes, being hypersensitive, are lysed *in vivo* by P.P.D. in a manner analogous to that observed *in vitro* by Favour. The lymphocytic reaction of tuberculous animals to P.P.D. was dependent upon the hypersensitive state since rabbits sensitized with dead tubercle bacilli react in a manner similar to the tuberculous rabbits. It is suggested that this lymphocytic response to P.P.D. may be the cause of the observed lymphopenia in progressive tuberculosis and may play a role in the delayed cutaneous reaction.

ANTITHYROTROPE AND ANTIGONADOTROPE ACTIVITY OF PARAHYDROXYPROPIOPHENONE IN HUMANS. *Roberts M. Rees, M.D. (by invitation) and William H. Beierwaltes, M.D., Ann Arbor, Mich.*

Parahydroxypropiophenone has been reported in the French literature to be an effective synthetic pituitary thyrotrope and gonadotrope inhibitor.

Five euthyroid postmenopausal women were subjected to control studies consisting of three consecutive quantitative follicle-stimulating hormone (FSH), basal metabolic rate (BMR), plasma cholesterol and serum protein-bound iodine (PBI) determinations. Each patient was then given 1 gm. of p-hydroxypropiophenone orally each day for two weeks, then 2 gm. daily for two more weeks. The above indices of TSH and FSH function were repeated at weekly intervals during therapy and at three days and seven days after cessation of therapy. The data showed a trend consisting of increasing TSH effect (increasing PBI and BMR and decreasing plasma cholesterol) and a concurrent decreased FSH effect. During the next two weeks of drug administration these values returned to baseline, with occasional overshoot.

In addition to these observations on euthyroid individuals, six patients were studied who had disease states presumably associated with increased TSH production. Three had malignant exophthalmos and three had exophthalmic goiter. Control exophthalmometer measurements, plasma cholesterol, PBI and radioactive iodine uptake determinations were done before and after p-hydroxypropiophenone administration for a period of one to four months. No

change occurred in the clinical state nor in the above laboratory indices of TSH function in these patients.

METABOLISM OF FRUCTOSE IN THE LIVER OF NORMAL AND DIABETIC SUBJECTS. *J. W. Craig, M.D. (by invitation), W. R. Drucker, M.D. (by invitation), Max Miller, M.D., J. E. Owens, M.D., B. Brofman, M.D. (by invitation), W. H. Pritchard, M.D. and H. Woodward, Jr., B.S. (by invitation), Cleveland, Ohio.*

Cori has shown by liver slice studies that the phosphorylation of fructose is catalyzed by a separate hexokinase and that fructose utilization is independent of glucose utilization. Hepatic vein catheterization studies were performed in two diabetic and three normal subjects in order to evaluate the role of the liver in the metabolism of fructose *in vivo*.

Hepatic venous and femoral arterial blood samples were obtained before, during and following intravenous administration of fructose (1 gm./kg.). These were analyzed for fructose, glucose, pyruvic, lactic, citric and malic acids. Using the BSP method for hepatic blood flow, net splanchnic assimilations were calculated.

The response to fructose of the diabetic patient deprived of insulin was similar to that of the normal subject. The liver rapidly removed fructose from the blood; approximately half of the administered fructose was taken up by the liver during the period of administration. Pyruvic and lactic acids were removed in small quantities during the control period, but during fructose infusion the concentrations of these two acids in the hepatic vein were much higher than in the artery. Citric and malic acid metabolism was not altered by fructose administration.

These studies indicate that (1) the liver plays an important role in the removal of fructose from the blood and converts a significant quantity to pyruvate, presumably by way of the Embden-Meyerhof scheme, and (2) the liver of the diabetic subject, in the absence of insulin, metabolizes fructose in the same manner as does the liver of the normal individual.

INEFFECTIVENESS OF DESOXYCORTICOSTERONE ACETATE IN INHIBITING THE DEPRESSION OF BLOOD EOSINOPHILS IN PATIENTS RECEIVING INSULIN-SHOCK THERAPY. *Hyman J. Zimmerman, M.D., John R. Walsh, M.D. (by invitation), Richard B. Johnson, M.D. (by invitation) and Fred Humoller, M.D. (by invitation).* (From the Department of Medicine and Research Laboratory, Veterans Administration Hospital, Omaha, Neb.)

The increase in insulin sensitivity occurring in rats after the administration of desoxycorticosterone has been attributed to the demonstrated ability of this steroid to inhibit the output of ACTH. An increase in sensitivity to insulin has also been demonstrated in insulin-insensitive human diabetes mellitus after the administration of desoxycorticosterone acetate. In an attempt to evaluate the role of adrenocortical inhibition in this phenomenon, studies were made of a group of psychiatric patients receiving insulin-shock treatment. Total eosinophil counts were obtained initially and five hours after the administration of insulin. The results obtained in patients pre-treated with desoxycorticosterone were compared with those in patients not receiving this steroid.

The twenty determinations in patients receiving insulin but not desoxycorticosterone showed a profound drop in the total eosinophil level ranging from 70 to 90 per cent of the control value. Although there was wide variation in the resting eosinophil level from day to day and from patient to patient, the insulin-induced eosinopenia was seen in all. The intramuscular administration of desoxycorticosterone either as a single dose of 10 mg. twelve hours before the insulin was given, or as a daily dose for varying periods up to fourteen days was completely ineffective in preventing the eosinopenia in an equal number of determinations.

The inability of DCA to inhibit the eosinopenia developing in patients receiving insulin-shock therapy may mean that this steroid fails to inhibit the release of ACTH in humans. The significance of these results will be discussed.

FREQUENT GOOD REMISSIONS IN PREVIOUSLY UNRESPONSIVE EYE DISEASES THROUGH INDIVIDUALIZED INTENSIVE TREATMENT WITH LONG-ACTING ACTH. *James R. Quinn, M.D. (by invitation) and William Q. Wolfson, M.D.* (From the Department of Ophthalmology and the Rackham Arthritis Research Unit, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.)

Short courses of ACTH or cortisone at conventional dosages have been discouraging in inflammatory disorders of the posterior ocular segment and optic nerve, particularly when chronic. Twenty-six patients, chiefly with poor initial prognosis, have received intensive long-

acting ACTH treatment with dosage level and treatment duration adjusted entirely according to responses of each individual patient. Special technics for adjusting dosage to requirements and for prophylaxis against side effects will be described. Results indicate the unconventionally high daily and total ACTH dosages required, the high percentage of good remissions, and the complete absence of relapses in patients who achieved satisfactory remission.

SODIUM RETENTION IN PATIENTS WITH ASCITES DUE TO CIRRHOSIS OF THE LIVER. *R. H. Moser, M.D. (by invitation), B. D. Rosenak, M.D., R. D. Pickett, M.D. (by invitation) and C. Fisch, M.D. (by invitation), Indianapolis, Ind.*

Parallel with our studies of the effect of cation exchange resins and water retention due to cirrhosis of the liver, we determined the urinary sodium output in nineteen cirrhotics manifesting ascites and/or edema. The patients studied were in-patients of the Indianapolis General Hospital. The clinical and laboratory findings justified the diagnosis of cirrhosis of the liver; in fifteen the diagnosis was confirmed histologically. Upon admission to the hospital the patient was placed on 1.5 gm. sodium diet and after a lapse of three days, three consecutive twenty-four-hour urine specimens were collected. The sodium content was determined by means of a Beckman flame photometer.

In ten patients the total urinary sodium output for twenty-four hours was less than 7 mEq. In another four patients the sodium output was below 26 mEq. per twenty-four hours. In one the output was 40 mEq. and in the remaining four the output was over 50 mEq. per twenty-four hours.

Our results suggest that sodium retention is an important part of ascites and edema formation in the cirrhotics. Some patients with cirrhosis of the liver manifesting water retention do not show parallel decrease in urinary sodium output. In these patients factors other than sodium retention are responsible for the positive water balance.

EFFECTS OF ADRENALINE UPON RENAL FUNCTION AND ELECTROLYTE EXCRETION. *J. F. Hammarsten, M.D. (by invitation), B. I. Heller, M.D. and W. E. Jacobson, M.D., Minneapolis, Minn.*

The reduction of the renal blood flow and glomerular filtration rate by the subcutaneous and intravenous administration of adrenaline has been adequately described. However, the effects of this renal ischemia and hypofiltration upon electrolyte excretion has not been investigated. Adrenaline was infused by a constant injection syringe to twelve young men without evidence of cardiovascular or renal disease. Renal hemodynamics, serum electrolytes and urinary electrolytes were determined before and during the adrenaline infusion. The usual pattern of diminished renal plasma flow and filtration rate and an increased filtration fraction was found. The urinary excretion of sodium, chloride and potassium was markedly reduced. The correlation coefficient for per cent change in glomerular filtration rate and per cent change in urinary sodium excretion was highly significant (+0.843). The serum sodium and chloride remained constant but serum potassium decreased. The alteration of serum potassium was not correlated with changes in renal function or with urinary excretion and reflected an intracellular shift of the ion.

The mechanisms involved in electrolyte excretion are discussed. The evidence indicates that tubular reabsorption cannot be evaluated as an independent entity in the presence of a changing filtration rate.

TRANSFER OF ELECTROLYTES ACROSS THE NORMAL URINARY BLADDER. *R. E. Nelson, M.D. (by invitation), C. J. Hlad, Jr., M.D. (by invitation) and J. H. Holmes, M.D.* (From the Department of Medicine and Surgery and the Radioisotope Laboratory, Denver VA Hospital and the Department of Medicine, University of Colorado School of Medicine, Denver, Colo.)

This investigation was undertaken to study factors influencing transfer of electrolytes across the normal urinary bladder membrane. Under nembutal anesthesia both ureters of dogs were isolated for urinary collections. Radioisotopes of sodium, chloride and phosphorus were introduced into the bladder and the rate of uptake and excretion determined over a six-hour period from blood and urine samples. The rates of transfer of sodium and chloride were similar, but phosphorus differed in that the intitial uptake was more rapid and the total amount transferred was much less. The rate of exchange was significantly altered by changes in pH. For example, with radioactive sodium 9 per cent transfer was noted at pH 5; 4.5 per cent at pH 6; 1.5 per cent at pH 7; and 2 per cent at pH 8. These values were calculated on the basis of total amount in the circulating plasma; when

calculated on the basis of extracellular volume the values were increased three to four times. Studies were made on the effect of change in concentration on the transfer of isotopes, keeping these changes within the urinary variations. The possible difference between the use of water and urine as the diluting fluid was investigated. The problem of absorption of urinary electrolytes through the bladder under various clinical and pathologic situations will be discussed.

RENAL PAPILLARY NECROSIS. *Arne Knutsen, M.D. (by invitation), Elmer R. Jennings, M.D., Arnold R. Axelrod, M.D. and Osborne A. Brines, M.D. (by invitation).* (From the Departments of Pathology and Medicine, Wayne University College of Medicine and the City of Detroit Receiving Hospital, Detroit, Mich.)

The clinical and pathologic findings in sixteen cases of renal papillary necrosis are presented. The diagnosis was established at necropsy in fourteen cases, by nephrectomy in one and by the histologic examination of a necrotic renal papilla recovered from the urine in the other. Eleven of the patients were diabetics; four had chronic obstructive uropathy. The clinical features not diagnostic but suspicious were: fever, neutrophilia, pyuria with or without hematuria, flank pain and, terminally, uremic coma with or without septicemia.

Characteristic gross pathologic manifestations were: (1) well demarcated pale yellow lesions involving the renal papillae often extending into the adjacent pyramids and surrounded by a hemorrhagic zone of reaction; (2) limitation of the lesion to the medulla; (3) multiplicity of lesions; (4) bilaterality; (5) normal or increased weight of involved kidneys. Conspicuous histologic features were: (1) sharply circumscribed zones of ischemic necrosis resembling infarction; (2) bacterial masses in necrotic tissue; (3) arteriosclerosis and arteriolosclerosis of moderate to severe degree; (4) lack of constant alteration in glomeruli and tubules; (5) paucity of thrombotic phenomena to account for the infarct-like necrosis.

The theories of pathogenesis are discussed. The proposed concept of a reverse Trueta shunt mechanism in the production of papillary necrosis is not supported by this study. Acquired renal ischemia due to vascular disease appears to be the most important factor in pathogenesis. Normal relative ischemia of the renal papilla and adjacent pyramid apparently localizes the lesion to its characteristic site.

Case Report

Marfan's Syndrome*

A Report of Three Cases with Aneurysm of the Aorta

JOHN THOMAS, M.D.,† G. B. BROTHERS, M.D.,
R. S. ANDERSON, M.D. *and* J. R. CUFF, M.D.
Nashville, Tennessee

MARFAN'S syndrome,[1] later described by Achard[2] as arachnodactyly, is characterized by slender, gracile extremities, relaxation of the ligaments, loss of subcutaneous fat and poorly developed hypotonic musculature. Since the original description other manifestations have been observed. These include congenital bilateral dislocation of the ocular lens, congenital cardiovascular abnormalities, dolichocephaly, high arched and cleft palate, prominent ears, asymmetry and deformity of the thoracic cage, maldevelopment of the lungs, subluxation of the joints and deformities of the feet.

In the first report of this entity published in the American medical literature Piper and Irvine-Jones[3] emphasized the frequency of cardiac lesions. In 1943 Baer, Taussig and Oppenheimer[4] described aneurysm of the aorta in this syndrome. They reported aneurysmal dilation of the aorta in two adults. Since then eleven cases of aortic aneurysm,[5–12] have been reported in association with arachnodactyly. Of these, seven were complicated by a dissecting aneurysm. (Table I.)

The following three cases emphasize the fact that aneurysm of the aorta is a serious complication of Marfan's syndrome. Likewise, dissecting aneurysm of the aorta frequently causes death in adult patients.

CASE REPORTS

CASE I. R. W., a thirty-two year old Negro male, entered Hubbard Hospital January 11, 1951, with the complaint of marked dyspnea. Except for slight exertional dyspnea he had previously been asymptomatic. Four weeks before admission he was seized with a severe, sharp, precordial pain which radiated to the epigastrium. He perspired profusely, became faint, fell to the floor but did not lose consciousness. The pain was unrelieved for two days in spite of medication. The dyspnea progressed and he became orthopneic. One week prior to admission swelling of the lower extremities appeared even though he was at bed rest.

The patient's mother had been told that he had heart disease when he was a child. At the age of eleven he was found to have bilateral dislocation of the ocular lenses. No heart lesion was noted at that time. Although he was 5 feet, 3 inches tall, he weighed only 78 pounds. The family history was significant in that an aunt had physical characteristics similar to those of the patient.

On physical examination blood pressure was 150/30, pulse 124 per minute, temperature 99°F. and respiration 40 per minute. The patient was apprehensive, cyanotic and markedly orthopneic. His physical build was striking. His height was 6 feet, 4 inches and he weighed only 148 pounds. The arms, fingers, feet and toes were extremely long and slender. There was marked genu valgus. All of the joints were hypermobile. The head was dolichocephalic. The pupils were small and were not dilated by homatropine. Both lenses showed temporal dislocation. The ears were prominent. The teeth were irregularly spaced. The palate was high and arched. The thoracic cage was long, narrow and tended to be of the "pigeon chest" type. The entire precordium was heaving and there were diastolic thrills at the base and apex of the heart. The cardiac dullness was increased both to the right and left of the sternum. At the aortic area a high-pitched, early diastolic and a soft systolic

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murmur were heard. At the apex a rumbling, low-pitched diastolic murmur was present. There were numerous moist rales throughout both lung fields. The liver was moderately enlarged and tender. There was 4+ pitting edema of the lower extremities.

in lead V4 was diphasic. X-ray examination of the chest (Fig. 1) revealed marked generalized cardiac enlargement and pulmonary congestion.

The patient failed to respond to efforts to relieve his congestive failure. He expired on the fifth hospital day.

TABLE I

CASES OF ANEURYSM OF THE AORTA OCCURRING IN MARFAN'S SYNDROME

Authors	Age, Sex and Race	Aneurysmal Dilation	Dissecting Aneurysm	Remarks
Baer et al.[4] 1943	25, M, N	+	0	Died (autopsy)
	13, F, W	+	0	Died (autopsy)
Etter and Glover[5] 1943	21, M, W	?	+	Died (autopsy); authors suggest that there was aneurysmal dilation of the aorta but the evidence presented was not convincing; ruptured into the pericardial sac
Parker and Hare[6] 1945	33, M, W	+	0	Alive at time of report
Tobin et al.[7] 1947	22, M, W	+	+	Died (autopsy); ruptured into pericardial sac
	35, F, W	0	+	Died (autopsy)
Strayhorn and Wells[8] 1947	28, M, W	+	0	Died autopsy); heart weighed 1,130 gm.
	28, F, W	+	0	Saccular aneurysm of ascending aorta; died suddenly at home
	29, F, W	+	0	Died at home
Uyeyama et al.[9] 1947	22, M, Japanese	+	+	Died (autopsy); x-ray showed aortic shadow progressively increased in size prior to dissection
Spickard[10] 1948	52, F, W	0	+	Died (autopsy)
Lindeboom and Bauwer[11] 1949	23, F, W	0	+	Died (autopsy); was pregnant; renal cortical necrosis; dissection involved the renal arteries
CPC, Massachusetts General Hospital[12] 1950	28, F, W	0	+	Died (autopsy)
Present report	32, M, N	0	+	Died (autopsy)
	26, M, N	+	+	Died (autopsy)
	35, F, N	+		Alive at time of report

Laboratory data were as follows: There was 1+ albuminuria; serum NPN, 62 mg. per cent; Kahn and Hinton tests, negative; white blood cells, 11,100 with a normal differential count; hemoglobin, 13 gm.; hematocrit, 40 per cent; sedimentation rate, 20 mm. (Wintrobe). Electrocardiogram showed abnormally wide P waves in leads I and II. The T wave in lead I was low and

Pathologic findings were as follows: The mediastinum was occupied by an enlarged heart 19 cm. in diameter. It touched the left chest wall and extended to within 3 cm. of the right chest wall. It weighed 800 gm. and was unusually flabby. There were many large areas of epicardial fibrosis over the upper portion of the right ventricle. Multiple petechiae were noted

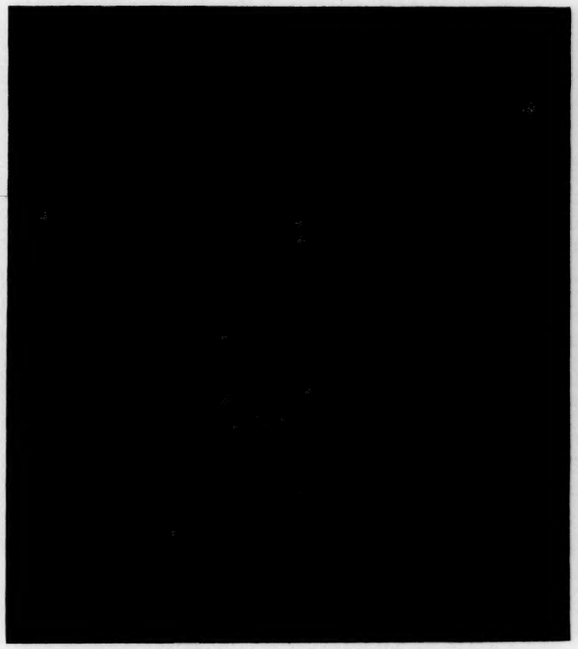

FIG. 1. Case I. X-ray of chest showing the marked globular enlargement of the cardiac silhouette and pulmonary congestion. Pericardial cavity contained 350 cc. of serous fluid.

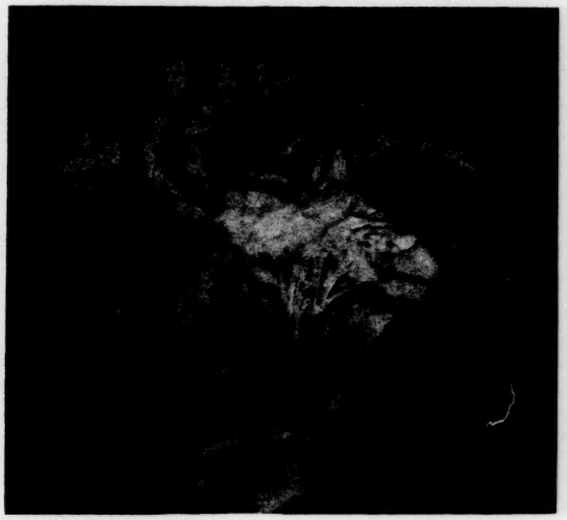

FIG. 2. Case I. Heart and portion of aorta showing a transverse rent just above the aortic valves which is the origin of the dissection.

along the larger vessels of the left ventricle. The epicardium was smooth. The coronary vessels showed only slight thickening in their proximal portions. The endocardium showed varying degrees of calcification in both the mitral valve area and the commissures of the aortic valve. Two centimeters distal to the aortic valve there was an 8 cm. transverse rent in the aorta. (Fig. 2.) This communicated with a continuous dissection along the aorta to a point 1 cm. above the origin of the renal arteries. At this point the dissection re-entered the lumen of the aorta. In spite of the marked dilation the aortic cusps were intact and the coronary openings were widely patent. The intimal surface of the aorta was thickened.

Microscopic examination of the aorta revealed an area of dissection within the media approaching the adventitia. The substance of the aorta in adjacent areas showed serous and mucinous cysts. In some of these endothelization of the walls had occurred. Although some sponginess of the pulmonary artery was noted, mucinous degeneration was not obvious.

Diagnoses: (1) cystic medionecrosis of the aorta; (2) recent dissecting aneurysm of the aorta; (3) cardiac hypertrophy and dilation; (4) deforming mitral and aortic valvulitis; (5) multiple hemorrhagic infarcts of lungs and liver; (6) congestion of lungs, liver and spleen; (7) slight arteriosclerosis of aorta, pulmonary and coronary vessels.

CASE II. B. G., a twenty-six year old Negro male, was first treated in 1937 in the medical outpatient clinic of Hubbard Hospital. His symptomatology was that of congestive heart failure. Nineteen days later he entered the hospital complaining of severe precordial pain and dyspnea. This pain began twenty-four hours prior to admission and was initiated by a bowel movement. It radiated to the back and to the abdomen.

On physical examination the blood pressure was 170/58, pulse 86 per minute, respiration 28 per minute and temperature 98°F. The patient was tall and thin. There was a marked degree of orthopnea. The ears were prominent. The pupils were small. There was malalignment of the teeth. The border of cardiac dullness was increased to the left and right of the sternum. In the aortic area there was a high-pitched diastolic and a harsh systolic murmur. A loud, rumbling diastolic murmur was present at the apex. There were bilateral, moist pulmonary rales.

His family history was of interest in that one sister had arachnodactyly (Case III, this report). One brother died elsewhere but had many characteristics of this syndrome. The parent and two other siblings were apparently normal.

The blood Wassermann test was negative. The

FIG. 3. Case II. Aorta—low power photomicrograph reveals a portion of the dissected media. The opening contains clotted blood in which early organizing changes are noted. The adventitia is extremely edematous and the media has a spongy appearance.

FIG. 4. Case II. Aorta—high power photomicrograph reveals a portion of the undissected media in which a large number of perpendicularly distributed areas of mucinous degeneration appear. These are associated with necrotic muscle fibers. Elastic fibers are not obvious. A line of low grade inflammatory reaction is present in the adventitia (lower edge).

patient continued to complain of the same type of pain that was present on admission and died suddenly on the third hospital day.

Pathologic findings revealed the following: The mediastinum was occupied by a tremendously dilated heart. There were large emphysematous bullae in the lungs. The heart measured 17 cm. vertically and 19 cm. transversely. The right auricle extended 9 cm. to the right of the midline. A fusiform aneurysm extended from the proximal aorta to the arch. It measured 9 by 5.5 cm. On opening the aneurysm a circular necrotic defect 4 by 5 cm. communicated with the dissecting coat of the media and was the origin of the dissecting aneurysm. The heart

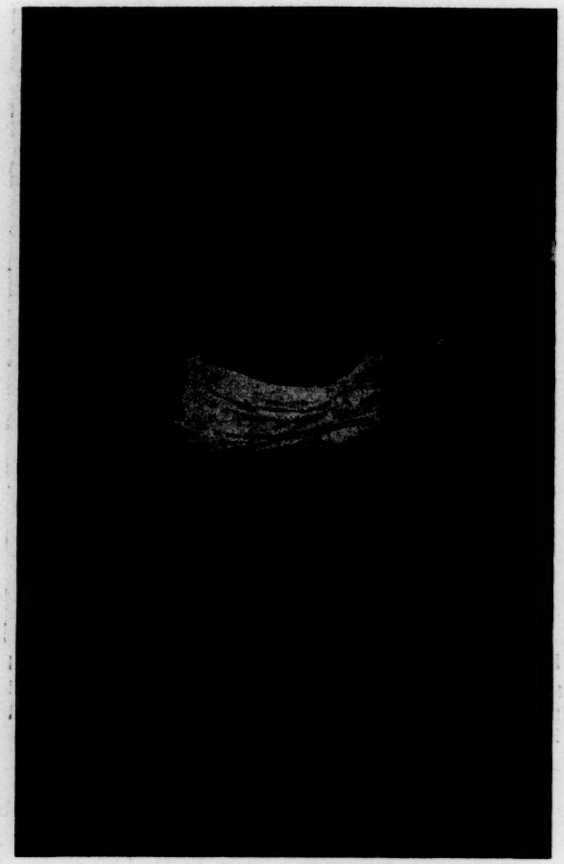

FIG. 5. Case III. This photograph demonstrates many of the characteristics of Marfan's syndrome. Note particularly the old facies, long narrow extremities and genu valgus.

weighed 760 gm. Several milky patches were present over the right ventricle anteriorly. Also there were recessive scarrings simulating healed infarcts which varied in size from 2 to 5 mm. and extended well within the musculature. The valves were slightly thickened but there was no vegetation. The aorta showed an extensive dissecting aneurysm from the arch to the bifurcation of the iliac vessels. In the thoracic aorta for a distance of 5 cm. there was a necrotic tear in the outer layer of the vessel. This was limited by the surrounding connective tissue.

Microscopic examination of the aorta (Figs. 3 and 4) showed the intima to be in a state of acute atheromatous thickening and a considerable amount of mucinous degeneration. Marked connective tissue reaction was noted. In one section a rent between the media and thickened adventitia was occupied by a recently formed thrombus. In some places there was definite evidence of organization. In certain areas this

defect split the media and in these regions considerable seepage of serum and red cells occurred.

Diagnoses: (1) Medionecrosis of the aorta; (2) dissecting aneurysm of the aorta; (3) fusiform aneurysm of the aorta; (4) hypertrophy and dilation of the heart; (5) pulmonary emphysema.

Case III. H. G., a thirty-five year old Negro female, was the sister of the previously described patient (Case II). When examined she had no complaints. Her past history revealed that she had delivered an apparently normal infant five months prior to this examination. She appeared much older than the stated age. Her height was 5 feet, 5 inches and she weighed 130 pounds. Blood pressure in both arms was 130/70. The body build was striking. (Fig. 5.) She was poorly developed and the arms, fingers and toes were extremely long and slender. There was kyphosis and genu valgus. Her head was dolichocephalic. The vision was normal and there was no dislocation of the lenses. The sternum was moderately depressed. There was an increase in aortic dullness to the left of the sternum. A soft systolic murmur was heard in the aortic area. The abdomen was protuberant and sagging. There was loss of subcutaneous fat. The fingers and toes were slender and gracile. The little fingers could be abducted at right angles to the hands. There was hypermotility of all joints.

Laboratory findings were as follows: Blood Wassermann test was negative. X-ray examination of the chest revealed aneurysmal dilation of the aorta. (Fig. 6.)

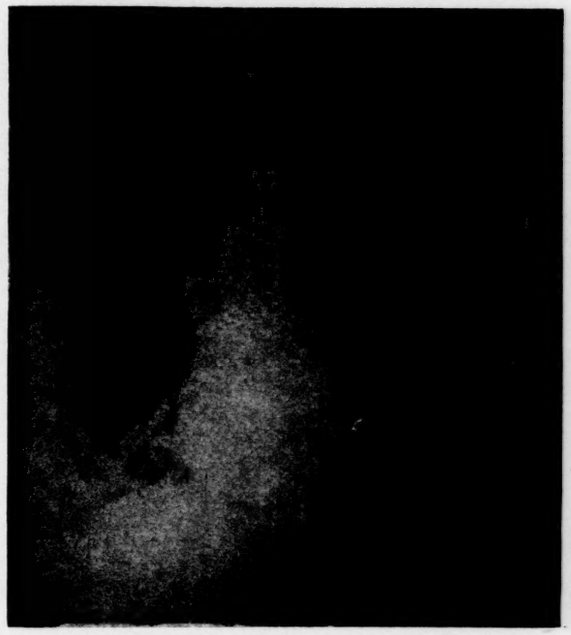

FIG. 6. Case III. X-ray of chest showing the aneurysmal dilation of the aorta.

COMMENTS

Although more than 200 cases of arachnodactyly have been reported, Tobin, Bay and Humphreys[7] were able to find descriptions of only twelve autopsied cases. In 1947 they reported two autopsied cases of patients who had a dissecting aneurysm of the aorta. Since then, including the two presented in this paper, there have been seven additional autopsied cases reported, making a total of twenty-one. Eight of these patients were less than twenty-eight months of age; no aortic lesion was found in this group. In the thirteen older patients there were nine in whom dissecting aneurysm of the aorta occurred. Three also had a fusiform aneurysm. Our cases constitute the eighth and ninth reported instances of dissecting aneurysm. All nine of the patients were adults. Eight of these were between twenty-one and thirty-six years of age and the ninth was fifty-two years of age.

The basic pathologic lesion in the aorta of the cases we have reported, cystic and mucinous degeneration of the media, is similar to that described in the literature. The resulting fusiform and dissecting aneurysms represent the most serious complication occurring in this syndrome. In those patients who reach adulthood it is frequently the underlying cause of early death.

SUMMARY

Three cases of arachnodactyly complicated by aneurysm of the aorta are presented. Two were dissecting aneurysms and one was a fusiform aneurysm.

A review of the literature reveals our cases to be the eighth and ninth to be reported in which dissection of the aorta occurred.

Aneurysm of the aorta is a frequent occurrence in arachnodactylic patients who reach adulthood. Dissection of the aorta may be responsible for early death in these patients.

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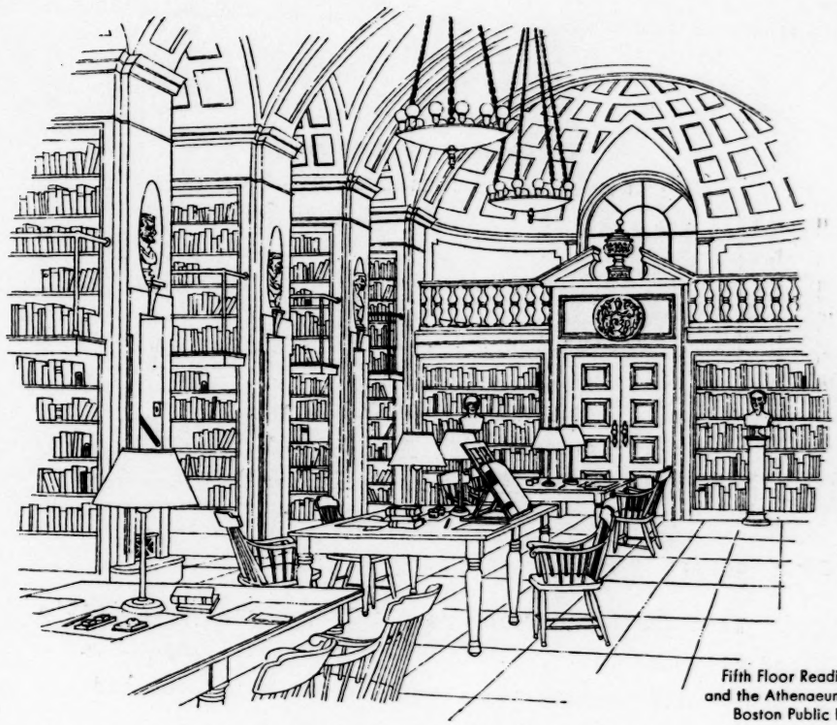

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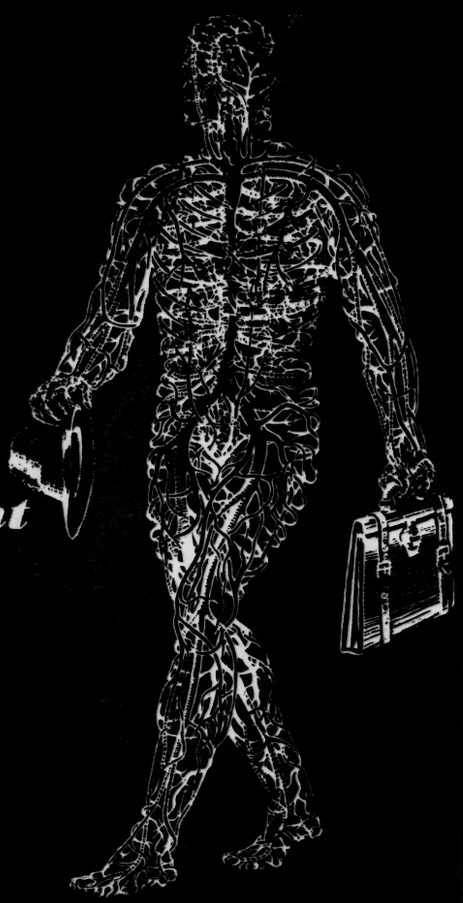

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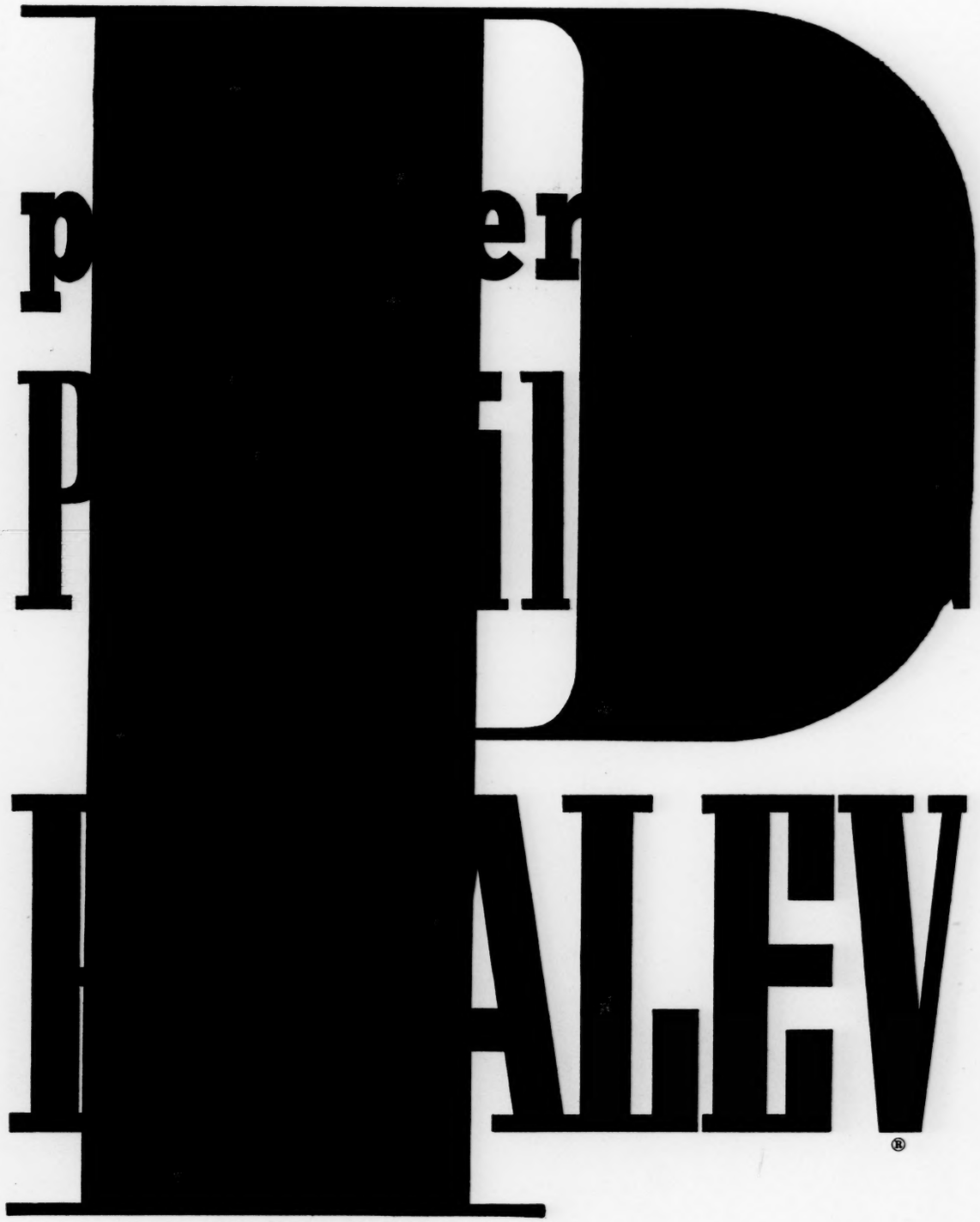

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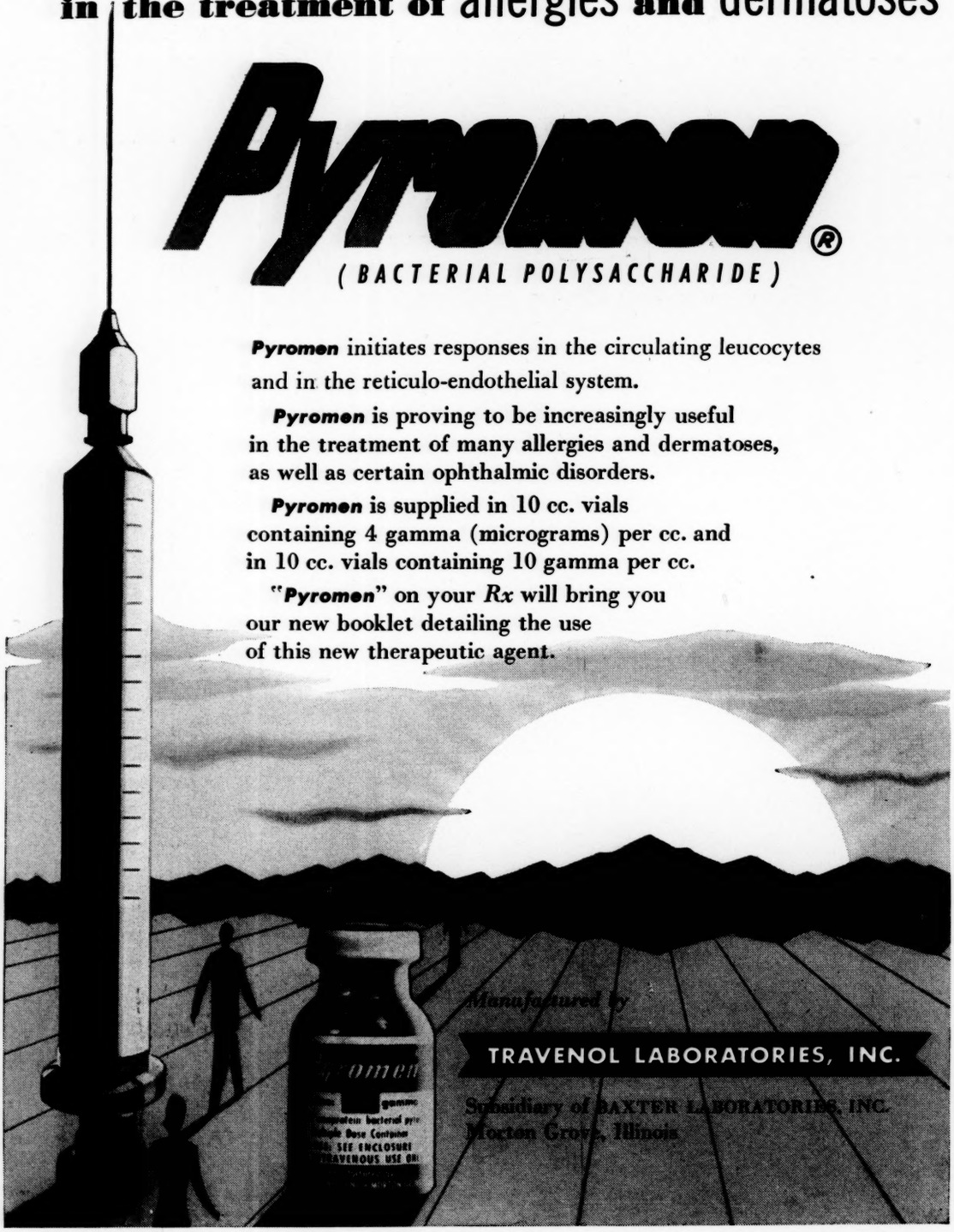

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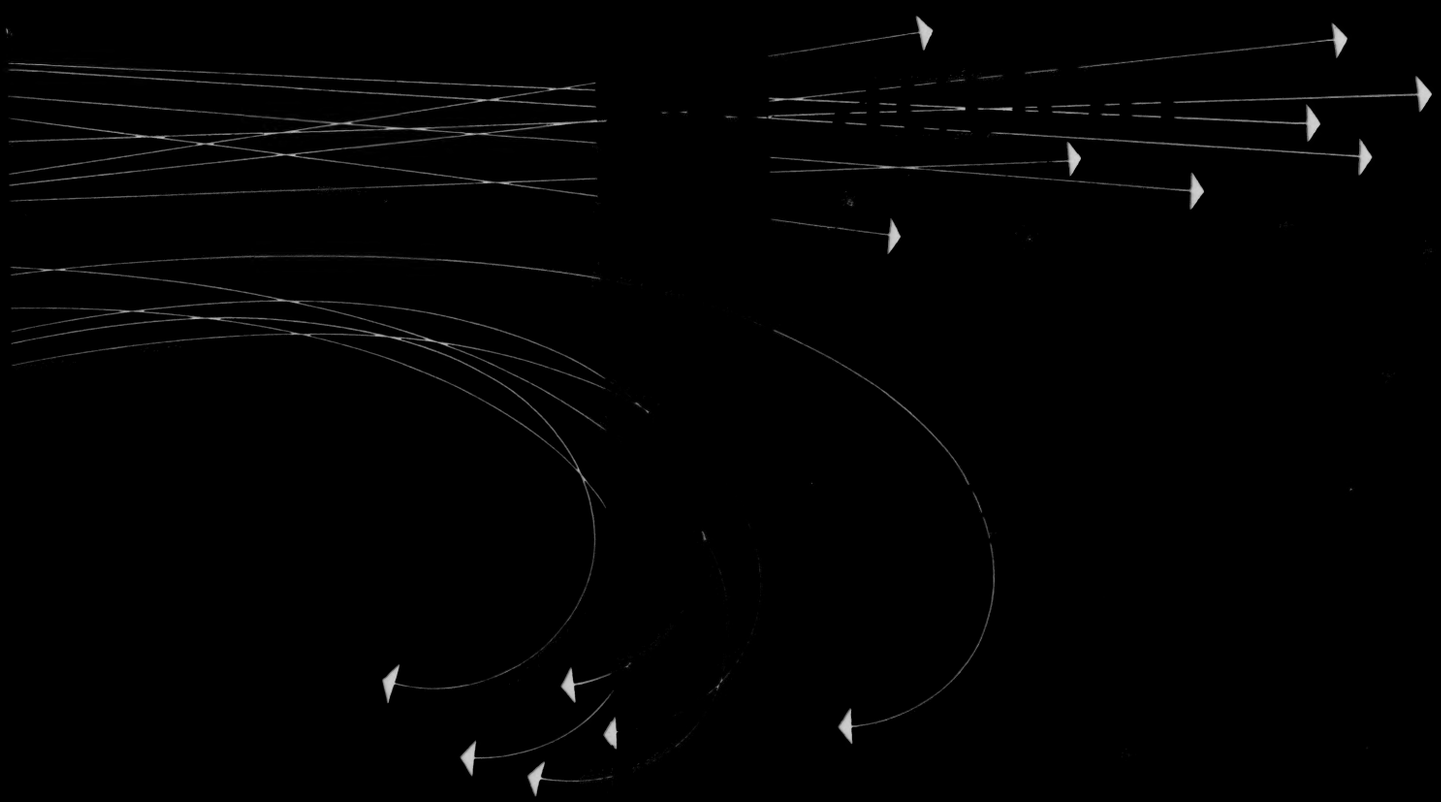

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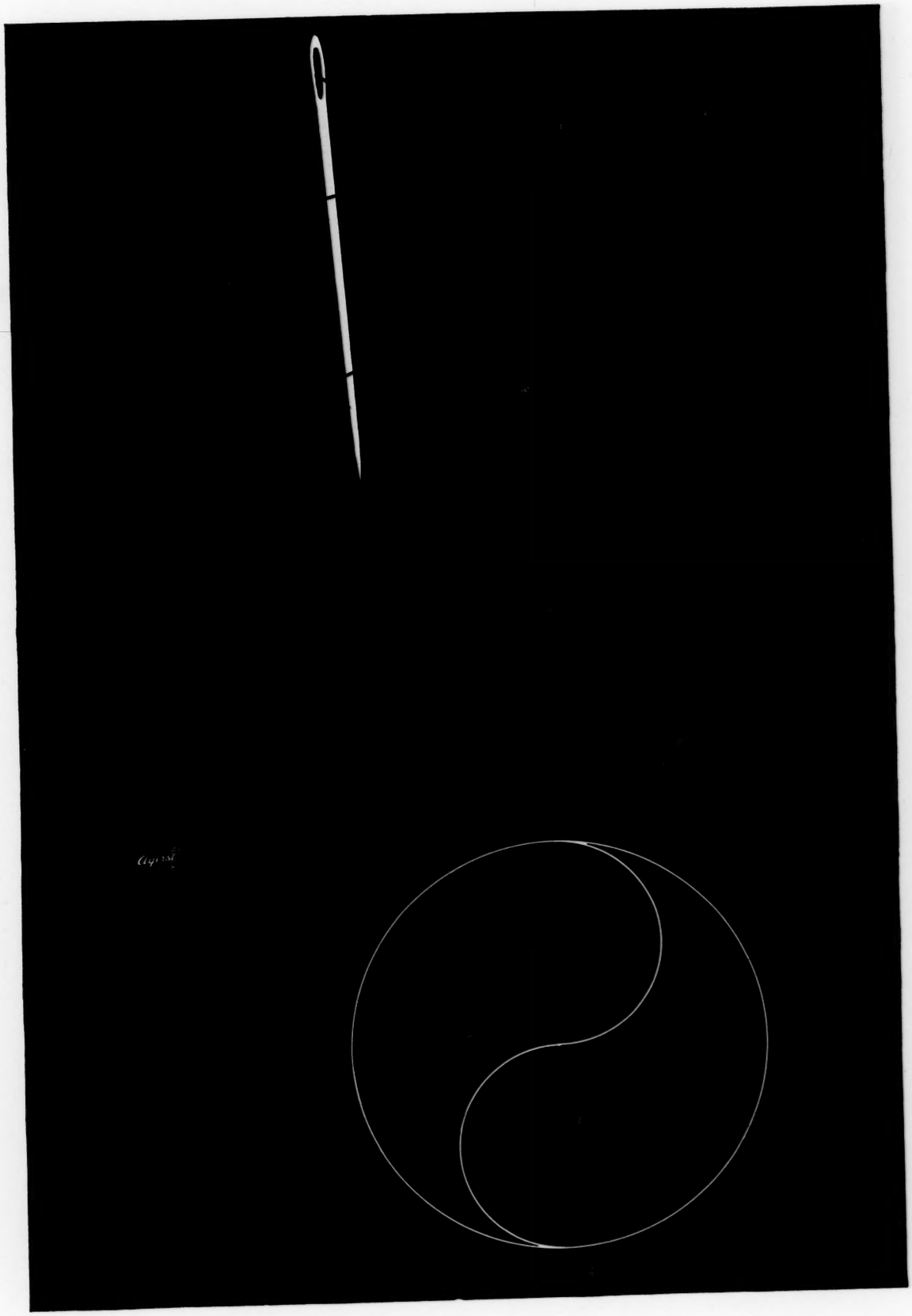

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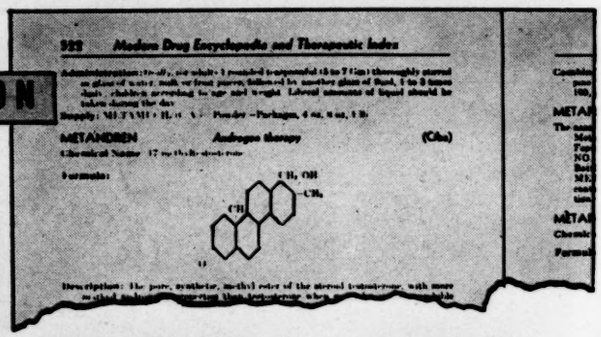

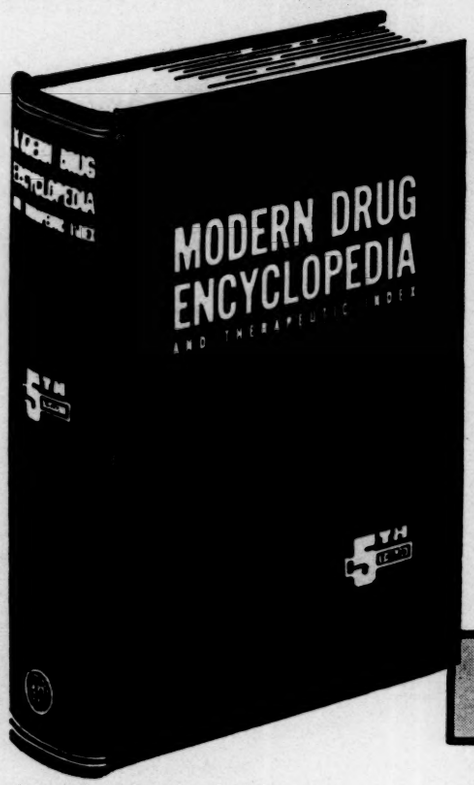

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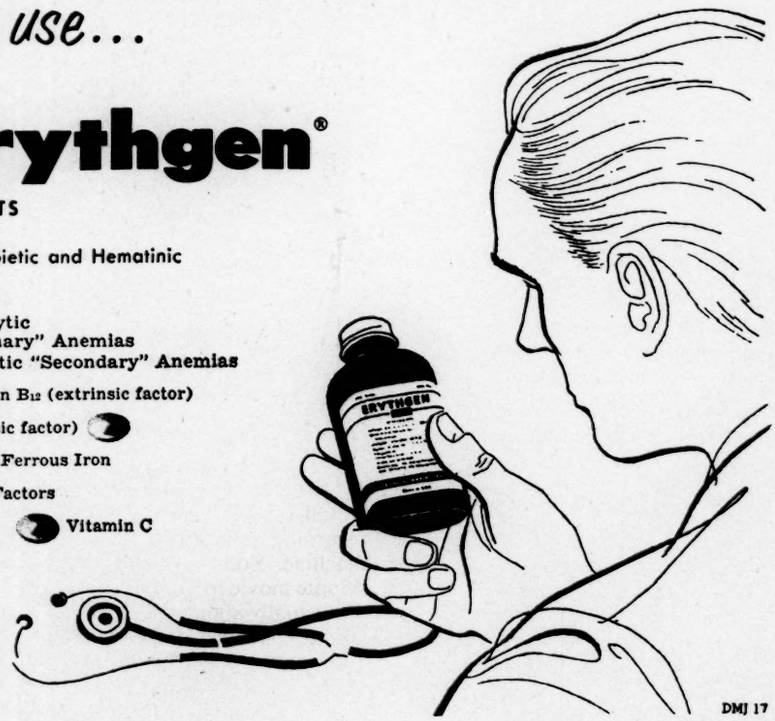

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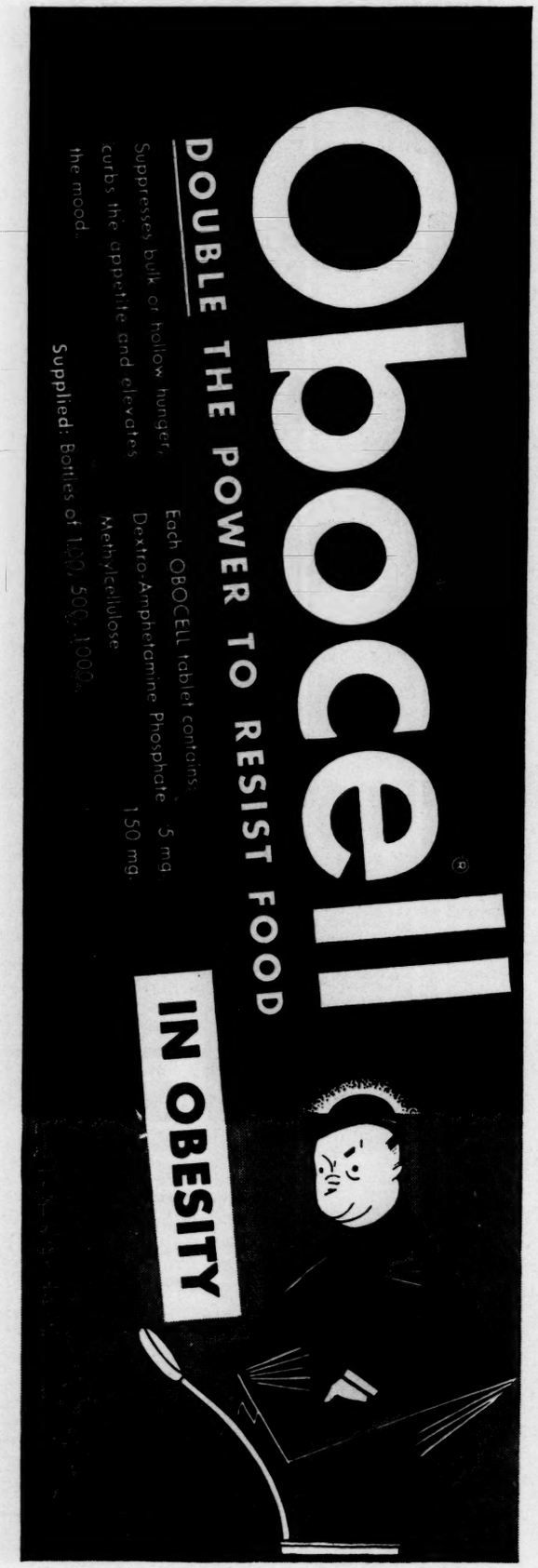

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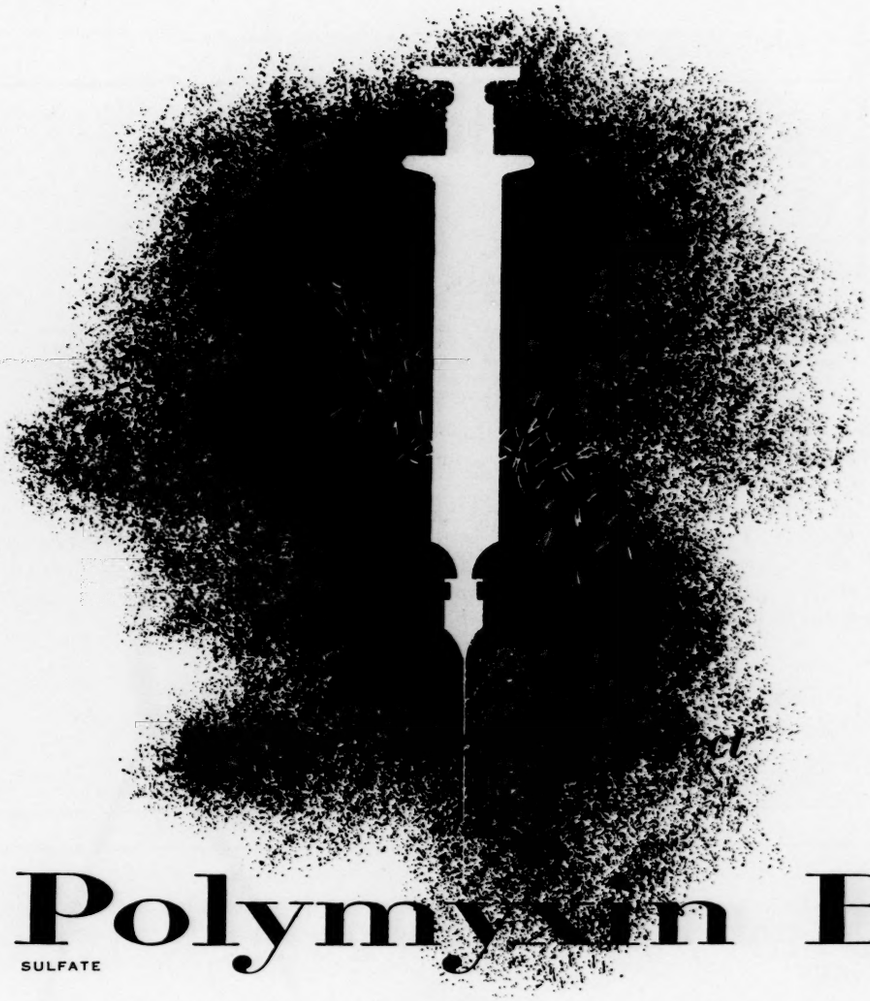

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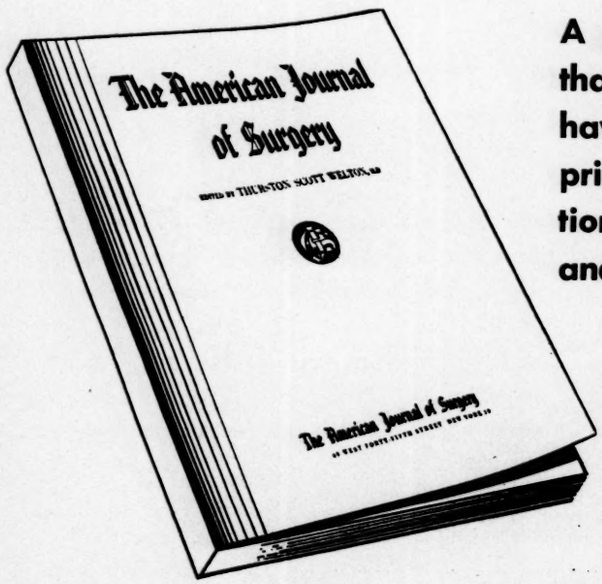

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